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## THE ROLE OF LONG-CHAIN OMEGA-3 POLYUNSATURATED FATTY ACIDS IN THE MANAGEMENT OF ROTATOR CUFF TENDINOPATHY

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**THE ROLE OF LONG-CHAIN OMEGA-3  
POLYUNSATURATED FATTY ACIDS IN THE  
MANAGEMENT OF ROTATOR CUFF TENDINOPATHY**

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**30<sup>th</sup> November 2015**

A thesis submitted for the degree of Doctor of Philosophy in the faculty of Science.

## Abstract

Rotator cuff (RC) tendinopathy is defined as pain and dysfunction of one or more of the RC tendons (supraspinatus, infraspinatus, subscapularis and teres minor). Inflammation has been associated with this condition. Graduated exercise is the main treatment for RC tendinopathy, and comparable outcomes to surgery, have been reported for the range of conditions associated with RC tendinopathy. However both non-surgical and surgical outcomes are frequently sub-optimal and new treatment methods to support current practice and improve outcomes are required.

A questionnaire investigation recruited 261 participants with shoulder pain from eight healthcare locations. Information was collected regarding beliefs and use of nutritional supplements. Supplement use was reported by 38% (100/261) respondents. Of those who were taking supplements, 82% (82/100) were taking them for shoulder pain. Fish oil supplements containing long-chain omega-3 polyunsaturated fatty acids (PUFAs) were the most popular dietary supplements.

Long-chain omega-3 PUFAs have been recommended for people with tendinopathy due to their potential to reduce inflammation. This investigation compared exercise and PUFAs to exercise and placebo supplements in the treatment of people with RC tendinopathy.

A double-blind placebo controlled randomized controlled trial was conducted in participants with RC tendinopathy recruited from hospital clinics. The active treatment group received nine opaque capsules of MaxEPA providing 1.53g eicosapentaenoic acid (EPA), 1.04g docosahexaenoic acid (DHA) and the placebo group received nine matching placebo capsules where the long-chain omega-3 fatty acids were replaced with oleic acid; all participants attended an eight week exercise programme. Participants were assessed, at pre-randomisation, eight weeks (primary outcome point), three months, six months and 12 months (secondary outcome point). Primary outcome was the Oxford Shoulder Score (OSS). Secondary outcomes included; the Shoulder Pain and Disability Index (SPADI), Patient Specific Functional Score, Euro Qol 5D-3L, Short Form 36, global rating of change and impairment measures. Analysis was by intention-to-treat. A total of 73 participants were randomized to treatment and data were available for the analysis of 36 in the PUFA supplement group versus 33 in the placebo. Both groups improved over the time course of the study. Plasma concentrations of EPA and DHA increased in the long-chain omega-3 PUFA supplemented group but not in the placebo, providing evidence that the participants took the supplements. There was no evidence of added benefit from long-chain omega-3 PUFA supplementation for the primary outcome change in OSS -0.23 (95% CI 3.89, 3.43) or in SPADI -1.68 (-12.64, 9.28) at two months. There was some evidence to suggest that SPADI was lower in the treatment group at three months. There was no difference in outcomes between groups at 12 months. Twelve participants undertook semi-structured face to face interviews to explore experiences, barriers, motivators and enablers to supplement use and exercise. The predominant enablers to exercise were found to be the perceived benefit from the exercises and extended follow up, with barriers being

lack of suitable equipment and pain. The enablers to supplement taking were found to be the perceived benefit of the supplements and a systematic pill taking routine. Barriers were the size, taste and quantity of supplements, remembering to take them, and, lack of perceived benefit.



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## **Acknowledgements**

I would like to take this opportunity to sincerely thank a number of people who have generously given their time, energy, support and expertise - without them this thesis would not have been possible.

My supervisors for their unstinting guidance and support: Professor Sanders, who kindly took me on a third of the way through, for his inspiration and assistance in guiding me through my discovery of the fascinating world of fatty acids; Dr Matthew Morrissey for supervision and advice during the initial stages of this project and Dr Jeremy Lewis for his mentorship, selfless support and encouragement throughout this challenging but enjoyable process. From the concept of the project, through every stage of the research process his help has been invaluable.

Robbie Gray for his technical assistance, help and advice; Dr Sarah Berry and Dr Dianne Reidlinger for their support and advice with various aspects of the studies; Hannah Dollings who assisted me when I was on maternity leave and without whom I could not have continued and Dr Abdel Douiri, King's College London, for his statistical advice.

The participants of the studies, who gave their time so generously and for their commitment to the scientific process.

The staff of the musculoskeletal physiotherapy departments at the referring sites for their assistance and enthusiasm in identifying participants to the project and for running the shoulder classes.

Seven Sea's Ltd, UK who provided the active and placebo supplements.

To them all - I remain sincerely grateful.

Above all, I thank my wonderful husband, Rob, whose love, patience and encouragement means so much; my mother and late father, whose continued support and belief in me has kept me going; my amazing friends and family who have supported me in so many ways and finally to my children - Isabella and Alasdair both born during this process – who have taught me so much already and to whom, I dedicate this thesis.

## Abbreviations

Abbreviation	Meaning
ALA	Alpha-linolenic acid
ARA	Arachidonic acid
bFGF	Basic fibroblast growth factor
BMI	Body mass index
BMR	Basal metabolic rate
BP	British Pharmacopeia
CI	Chief investigator
Cm	Centimetres
COX	Cyclooxygenase
DHA	Docosahexaenoic acid
DHLA	Dihomo-gamma linolenic acid
EFSA	European Food Safety Authority
EPA	Eicosapentaenoic acid
EQ 5D 3L	Euro QoL 5D 3L
FAME	Fatty acid methyl esters
FID	Flame ionization detector
GC	Gas chromatograph
GLA	Gamma-linolenic acid
GROC	Global rating of change
H <sub>2</sub> O <sub>2</sub>	Hydrogen peroxide
HHD	Hand held dynamometer
ICC	Intra class correlation
IL-1 $\alpha$	Interleukin-1 alpha
IL-1 $\beta$	Interleukin-1 beta

IL-6/8/10	Interleukin-6/8/10
iNOS	Inducible nitric oxide synthase
IQR	Interquartile range
Kg	Kilograms
LA	Linolenic acid
LBP	Low back pain
LOX	Lipoxygenase
LPS	Lipopolysaccharide
LT	Leukotriene
LTB <sub>4</sub>	Leukotriene B4
LTC <sub>4</sub>	Leukotriene C4
LTD <sub>4</sub>	Leukotriene D4
LTE <sub>4</sub>	Leukotriene E4
MCIC	Minimal clinically important change
MCID	Minimal clinically important difference
MID	Minimally important difference
MUFA	Monounsaturated fat
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHS	National Health Service
NRS	Numerical rating scale
NSAIDS	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OSS	Oxford shoulder score
PG	Prostaglandin
PGD <sub>2</sub>	Prostaglandin D2

PGE <sub>2</sub>	Prostaglandin E2
PSFS	Patient specific functional score
PUFAs	Polyunsaturated fatty acids
RA	Rheumatoid arthritis
RC	Rotator cuff
RCT	Randomised controlled trial
RNI	Reference nutrient intake
ROM	Range of motion
SD	Standard deviation
SDC	Smallest detectable change
SEM	Standard error of measurement or mean
SF 36	Short Form 36
SF 36 MCS	Short form 36 mental component summary
SF 36 PCS	Short form 36 physical component summary
SF 36 BP	Short form 36 bodily pain
SF 36 GH	Short form 36 general health
SF 36 MH	Short form 36 emotional well being
SF 36 PF	Short form 36 physical functioning
SF 36 RE	Short form 36 role limitations due to emotional health
SF 36 RP	Short form 36 role limitations due to physical health
SF 36 SF	Short form 36 social functioning
SF 36 VT	Short form 36 vitality
SPADI	Shoulder pain and disability index
TNF $\alpha$	Tumour necrosis factor alpha
UK	United Kingdom

UKUFF	UK National rotator cuff trial
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
WOMAC Score	Western Ontario and McMaster Universities Osteoarthritis Index



# **Chapter 1 : Introduction**

This thesis reviews the evidence for the efficacy of long-chain omega-3 polyunsaturated fatty acids (PUFA) in the treatment of rotator cuff (RC) tendinopathy. It explores the relationship between exercise, nutritional supplements and RC tendinopathy. A cohort of patients presenting with shoulder pain were surveyed about their attitudes to taking nutritional supplements. The potential role of long-chain omega-3 PUFAs in addition to exercise was investigated in the management of RC tendinopathy. The final stage of the study used qualitative methods to investigate the participants' experiences, barriers, motivators and enablers to nutritional supplement use and exercise in RC tendinopathy.

The primary function of the shoulder is to place the hand to perform a multitude of upper limb functional tasks requiring strength, power, endurance, stability and precision. The shoulder complex is the most mobile musculoskeletal region in the body. The RC muscles and tendons contribute both to stability and movement at the glenohumeral joint of the shoulder complex. The presence of pain and alterations in normal movement patterns often results in a substantial reduction in shoulder and subsequently upper limb function.

It is estimated that up to 67% of the population will experience shoulder pain at some point in their lives (Chard, Hazleman et al. 1991, Luime, Koes et al. 2004). In a survey of general practices in Cambridge, United Kingdom (UK) the incidence of shoulder pain was found to be 9.5/1000 (Östör, Richards et al. 2005). The high incidence of musculoskeletal conditions involving the shoulder has considerable socio-economic implications due to time lost from work and associated healthcare costs (Ekberg, Bjorkqvist et al. 1994, Virta, Joranger et al. 2012). In a recent study conducted in Sweden, the mean total annual cost of a shoulder injury was found to be €4139 per patient, with sick leave contributing 84% of those costs (Virta, Joranger et al. 2012). Disorders of the shoulder contribute to 30% of all occupational musculoskeletal pathologies, which is equal to the proportion due to cervical spine pathology (Nygren, Berglund et al. 1995). The incidence of shoulder pain substantially increases with age, rising to approximately 20% in individuals aged over 70 years (Chard, Hazleman et al. 1991). In contrast to prevalence, which describes the proportion of the population that has the condition at any one time (Jager, Zoccali et al. 2007), incidence describes the number of new cases or people acquiring the condition in the population.

The majority of shoulder pain is believed to arise from the peri-articular soft tissues, especially the RC, (Uthoff and Sarkar 1990, Östör, Richards et al. 2005). This view is supported by research examining people working in industry, those being treated in primary care and workers' compensation cases, which have demonstrated that RC tendinitis is the most frequent shoulder diagnosis, accounting for 85% of diagnoses made by general practitioners (van der Windt, Koes et al. 1996, Silverstein, Welp et al. 1998, Östör, Richards et al. 2005, Bishay and Gallo 2013).

The terminology used to describe disorders of the RC is inconsistent. This confuses understanding and can hinder comparison across research investigations. Chapter 2 reviews the terminology and explains why the term RC tendinopathy is used in this thesis.

RC tendinopathy is associated with long-term morbidity and loss of function. RC tendinopathy is considered the most common of all tendinopathies with the annual incidence being over 1% (Chaudhury, Gwilym et al. 2010, Tashjian 2012).

Exercise has been proven to be an effective treatment for RC tendinopathy with equivalent outcomes to surgery (Haahr and Andersen 2006, Ketola, Lehtinen et al. 2013). Although beneficial in reducing pain and improving function, many people completing a course of exercise therapy continue to experience pain and functional disability for up to one year (Ainsworth, Lewis et al. 2009, Holmgren, Bjornsson Hallgren et al. 2012, Lewis 2012, Litchfield 2013). The pain and functional disability is frequently long term, with over 50% of individuals experiencing on-going pain after three years (Macfarlane, Hunt et al. 1998).

Exercise therapy does not always lead to a complete resolution of symptoms for those diagnosed with RC tendinopathy and as a consequence of this, other treatments are also recommended by healthcare professions. Corticosteroid and platelet rich plasma injections are increasingly being used in the non-surgical management of RC tendinopathy. These injections have been shown to be beneficial in the short term but at a year's follow-up were shown to be no more effective than exercise (Hart 2011, Kesikburun, Tan et al. 2013). Similarly, in a recent review, surgery was found to be no more beneficial than non-surgical interventions (Tashjian 2013).

In light of the limited benefit afforded by treatment currently regarded as best practice, there is a need to identify new and novel methods for treating for this common and disabling condition. The potential benefit of an long-chain omega-3 PUFA and an anti-oxidant supplement in the treatment of athletes with a range of tendinopathies including; supraspinatus, biceps, medial and lateral epicondylar, patellar and infraspinatus tendinopathies was highlighted by Mavrogenis et al (2004). A significant reduction in pain was observed in the long-chain omega-3 PUFA and anti-oxidant treatment group and this was hypothesised to be as a result of the formation of signalling molecules (eicosanoids) with a less potent inflammatory action.

The dietary supplement market is a rapidly growing industry, with an annual UK turnover of in excess of £700 million, and sales are expected to reach £786 million by 2018 (<http://www.euromonitor.com/vitamins-and-dietary-supplements-in-the-united-kingdom/report>). It is estimated that 40% of UK adults regularly use dietary supplements (Mason 2007). Despite this widespread use their role and benefit in tendon-related disorders has come under little rigorous scientific scrutiny. Recently, their role, use and general efficacy have also been challenged in the popular press and media (Sanders 2012).

This thesis presents four interrelated studies, which aim to add to the knowledge base regarding the use of nutritional supplements in shoulder pain;

1. Reliability study investigating the intra- and inter-rater reliability of shoulder range of motion and strength (Chapter 6).
2. Survey of shoulder pain and the use of nutritional supplements: a questionnaire based investigation (chapter 7).
3. A double blind randomised controlled trial investigating the efficacy of long-chain omega-3 PUFAs and exercise in the treatment of RC tendinopathy (chapter 8).
4. Exploring experiences, barriers, motivators and enablers to nutritional supplement use and exercise in RC tendinopathy (chapter 9).

In order to be able to consider the potential beneficial effects of long-chain omega-3 PUFAs on RC tendinopathy it is first necessary to have a thorough understanding of RC tendinopathy and its pathophysiology. The following chapter will explore this topic in detail.

## **Chapter 2 : Rotator cuff tendinopathy**

### **Authors contribution to publication associated with this chapter**

The publication associated with this chapter (Appendix 11.29) in Journal of Hand Therapy was co-written with Jeremy Lewis. Jeremy Lewis was lead author as he formulated the concept and led the writing of the discussion. Fiona Sandford also reviewed the literature and contributed to the discussion, wrote the background, methods and summary sections. Fiona Sandford also assisted in the review process.

## **Introduction**

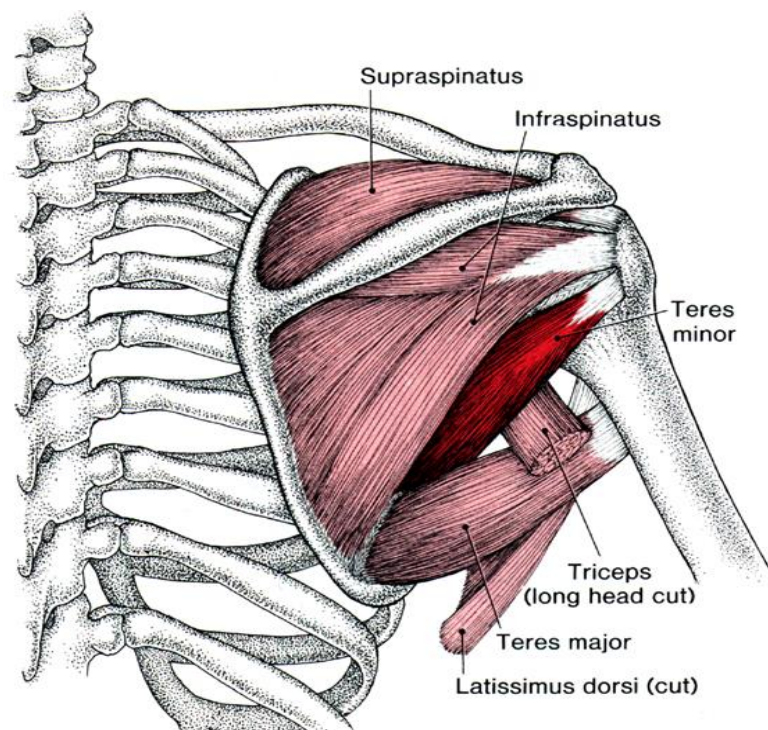
Establishing an understanding of the pathophysiological mechanisms of rotator cuff (RC) tendinopathy is crucial to comprehend why certain treatments might work and for guiding the development of new and novel treatments for the future. As such this chapter aims to:

- Provide an overview of anatomy and function of the shoulder and of the RC.
- Review the terminology associated with tendon related disorders of the RC.
- Discuss the aetiology of RC tendinopathy.

## **Anatomy and function of the shoulder**

The shoulder (Figure 2.1) is capable of the most extensive range of motion of any joint in the body (Quillen, Wuchner et al. 2004, Longo, Berton et al. 2011). Its primary role is to position the hand in order to facilitate upper limb function (Peat 1986, Myers and Lephart 2000). This function ranges from highly explosive overhead throwing actions (Anderson and Alford 2010) to positioning the hand in the field of vision for intricate prehensile activities for sustained periods of time (Peat 1986, Culham and Peat 1993). The upper limb is frequently used for activities involving weight bearing, such as during a push up, rock climbing and gymnastics, necessitating stability and resistance to compression at the glenohumeral joint. Additionally, when carrying a weight in the hand the shoulder needs to withstand forces that distract the shoulder. When shoulder function is compromised, substantial morbidity and disability follow (van der Windt, Koes et al. 1996, Winters, Jorritsma et al. 1999).

Figure 2.1 The shoulder complex and the rotator cuff



Chapter 23, Figure 23.3, Page 390 (Travell and Simons 1983). *Myofascial pain and dysfunction: The trigger point manual. Vol 1: The upper extremities*, Baltimore, Williams and Wilkins

The shoulder joint consists of three bones; the scapula, humerus and the clavicle and four articulations; the glenohumeral joint, the acromioclavicular joint, the sternoclavicular joint and the scapulothoracic mechanism (Culham and Peat 1993).

The glenohumeral joint is a multi-axial ball and socket joint comprising of the round humeral head and the shallow glenoid fossa of the scapula (Poppen and Walker 1976). In order to increase its joint surface area and stability without compromising the flexibility there is a fibrocartilaginous rim, the glenoid labrum surrounding the glenoid fossa (Cooper, Arnoczky et al. 1992).

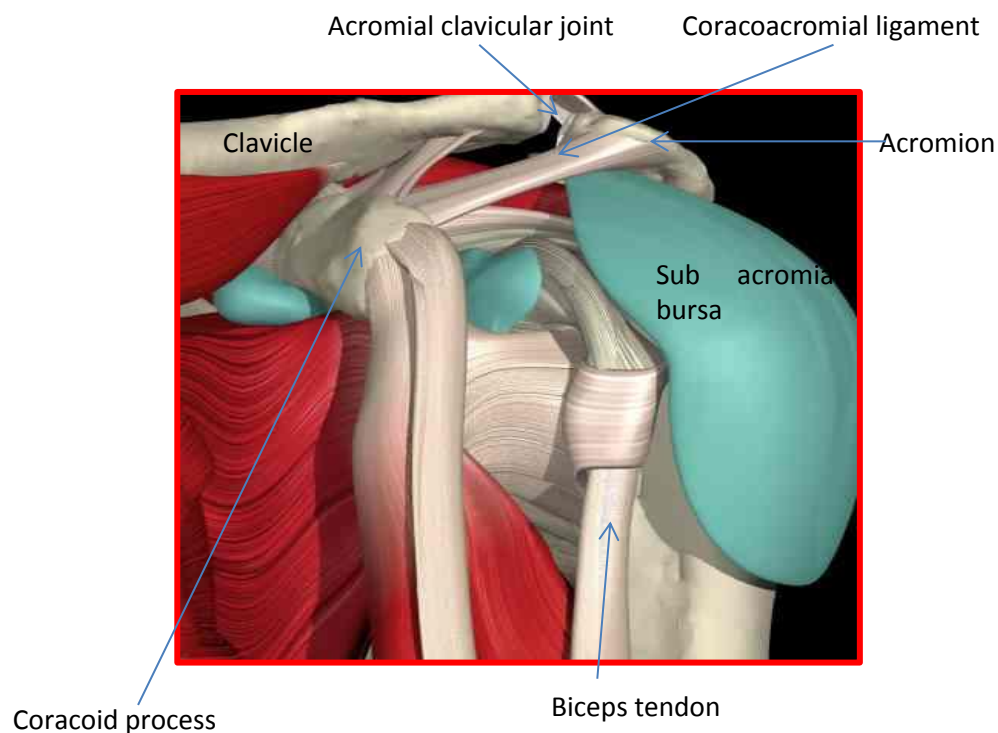
The acromioclavicular joint is a flat, gliding, synovial joint involving the articulation of the lateral end of the clavicle and the acromion process of the scapula. It provides additional flexibility and range of motion to the shoulder joint, which would not be possible with the glenohumeral joint in isolation, by allowing further rotation and adjustment of the scapula on the thorax. The acromioclavicular joint is also responsible for allowing the transmission of forces from the upper limb into the thorax and for suspending the upper limb (Lemos 1998).



The shoulder gains its static stability from its joint capsule and the surrounding glenohumeral, coracohumeral and coracoacromial ligaments (Ishihara, Mihata et al. 2013). The coracoacromial arch consists of the coracoacromial ligament, acromion and coracoid process of the scapula. The coracoacromial arch forms the roof of the subacromial space which is found above the glenohumeral joint. The superior aspect of the humeral head and the greater tuberosity of the humerus form the floor of the subacromial space. It is within this space that the subacromial bursa and the RC tendons are located (Standring 2005).

Bursae are synovial lined sacs which are situated over bony prominences or surfaces where tendon friction may occur (Hirji, Hunjun et al. 2011). Their function is primarily to reduce any friction during movement. Approximately ten bursae have been identified in the shoulder (Hirji, Hunjun et al. 2011). The largest and most substantial bursa in the region is the subacromial bursa (Figure 2.3). It is located in the subacromial space, between the RC tendons and the under surface of the acromion (Standring 2005). Normally there is no communication between the glenohumeral joint and the subacromial bursa (Hirji, Hunjun et al. 2011).

Figure 2.2 Sub-acromial bursa of the shoulder



Primal pictures (<https://www.primalpictures.com/>)

### **Anatomy and function of the rotator cuff**

The RC is the name given to a group of muscles and their tendons that contribute to movement and stability at the glenohumeral joint. The four muscles and tendons of the RC are the; supraspinatus, infraspinatus, subscapularis and teres minor (Clark and Harryman 1992). The tendons of the RC form a convergent insertion into the greater and lesser tuberosities of the humerus (Clark and Harryman 1992, Barr 2004, Curtis, Burbank et al. 2006). The long head of biceps tendon should be considered functionally as part of the RC, due to its location between the subscapularis and supraspinatus tendons and the inter-digitation of their fibres (Barr 2004).

Given the proximity of the RC muscles to the glenohumeral joint, they provide dynamic stability to the joint (Hess 2000), in flexion by controlling anterior translation of the humeral head by activating the posterior cuff and in the opposite in extension stopping posterior translation of the humeral head by activating the anterior cuff (Boettcher, Cathers et al. 2010, Sangwan, Green et al. 2014).

## **Terminology associated with tendon related disorders of the rotator cuff**

A lack of consistency exists within clinical practice and research regarding the terminology used to define shoulder conditions involving the RC. RC disease, tendinitis, tendinosis, tendinopathy, impingement and subacromial impingement and tears and are often used inter-changeably within the literature (Rees, Stride et al. 2013, Dean, Gettings et al. 2015). Without a clear, agreed definition, it is difficult to interpret and compare results of randomised controlled trials (RCTs) that investigate RC tendinopathy.

All terms essentially describe a similar clinical picture of pain and loss of shoulder function. The following section sets out to define these diagnostic terms.

### **2.1.1 Rotator cuff disease**

RC disease is an overarching term which does not implicate any specific tendon pathology. It is used to describe the clinical presentation of symptoms in the absence of histological and imaging findings.

### **2.1.2 Rotator cuff tendinitis**

Describes inflammation of the RC tendons (Bass 2012). The role of classic inflammation in the pathological process of RC disorders remains equivocal (Longo, Berton et al. 2011). Therefore tendinitis should only be used when a histological examination clearly demonstrates inflammation is present.

### **2.1.3 Rotator cuff tendinopathy**

RC tendinopathy is a clinical classification and relates to the symptoms of shoulder pain and loss of function without reference to pathology (Lewis 2009). Shoulder pain is provoked with load, either through lifting or through resisted muscle tests performed during an examination (Littlewood, Ashton et al. 2012).

### **2.1.4 Rotator cuff tendinosis**

RC tendinosis describes the degeneration of the RC tendons (Bass 2012) without the presence of inflammation. The term requires both imaging and histological confirmation and as such would be an inappropriate clinical diagnosis.

### **2.1.5 Sub-acromial impingement/ impingement syndrome**

This term is used to describe the mechanical compression and irritation of sub-acromial structures (including the tendon and muscle of the supraspinatus, long head of biceps tendon and the sub-acromial bursa) between the coraco-acromial arch and humerus during elevation of the arm above 90° (Neer 1972, Neer 1983). This mechanism of RC injury has been questioned (Lewis 2014) and there exists a body of evidence to refute its validity (Brox, Gjengedal et al. 1999, Haahr, Ostergaard et al. 2005, Haahr and Andersen 2006, Kukkonen, Joukainen et al. 2014, Lewis 2014).

### **2.1.6 Rotator cuff tears (partial or full thickness)**

A RC tear describes discontinuity of the tendon fibres of the RC tendon(s), most commonly involving the supraspinatus near to its insertion (Freygant, Dziurzynska-Bialek et al. 2014). RC tears are diagnosed with imaging modalities such as ultrasound and MRI, however, there is a poor association between pain and the presence of a tear or tear size (Tempelhof, Rupp et al. 1999, Dunn, Kuhn et al. 2014).

### **2.1.7 Subacromial bursitis**

Sub-acromial bursitis is a condition which is characterised by inflammation of the sub-acromial bursa. The only method of confirming this diagnosis is via biochemical analysis, and cannot be made by any clinical assessment procedure or imaging technique.

### **Use of tendinopathy in this thesis**

The biochemical and clinical terminology used to describe RC disorders have one unifying link in that they are used to detail a clinical picture: shoulder pain, made worse on movement and loading, especially with overhead activities and/or at night, commonly accompanied with weakness and loss of function. The pathological processes occurring within the tendon are not fully understood, nor are the causes and mechanisms of the pain. Treatment is often directed at the symptoms rather than the structural pathology and as such, it was decided that the term; tendinopathy, would be used within this thesis to describe the clinical presentation without any reference to the pathology.

## **Aetiology of rotator cuff tendinopathy**

Although extensive research on RC tendinopathy exists, the exact causative mechanisms remain elusive. There are a number of mechanisms which have been proposed as underpinning this condition. The local, pathological tendon based mechanisms (Cook and Purdam 2008), the central nervous system modulatory mechanisms (Littlewood, Malliaras et al. 2013) and the inflammatory mechanisms (Rees, Stride et al. 2013) will be discussed below because these are the mechanisms with most relevance to this thesis. Further understanding of mechanisms may assist researchers in developing improved treatment approaches more specifically directed at influencing them.

### **2.1.8 Possible local tissue pathological mechanisms underpinning rotator cuff tendinopathy**

Models that suggest the pain experienced in tendinopathy is due to tissue injury or structural pathology with subsequent noiceptive input and pain in proportion to the degree of injury have been proposed (Cook and Purdam 2008, Lewis 2009). However, there appears to be a disassociation between pathology and pain (Cook and Purdam 2008, Drew, Smith et al. 2014).

When comparing MRI findings in an aged-matched, symptomatic impingement syndrome group versus an asymptomatic group, Frost et al (1999) were unable to distinguish between the two groups based on the structural pathology. A RC tear also does not always equate to pain with asymptomatic tears in up to 40% of the general population and elite overhead athletes (Tempelhof, Rupp et al. 1999, Connor, Banks et al. 2003, Worland, Lee et al. 2003, Yamamoto, Takagishi et al. 2010). In addition, as clinical outcomes improve in response to exercise therapy, a corresponding change in the pathological structure of the tendon is not observed (Drew, Smith et al. 2014).

The lack of association between pain and pathology is a confounding factor in the local tissue pathology-pain mechanism model (Cook and Purdam 2008) and so additional explanations for the symptoms experienced in RC tendinopathy are now being sought. These include the involvement of the central nervous system (CNS) and inflammation.

#### **2.1.9 Possible central nervous system mechanisms underpinning rotator cuff tendinopathy**

The influence of the CNS has been widely recognised in other musculoskeletal conditions (Winkelstein 2004, Wand, Parkitny et al. 2011, Arendt-Nielsen, Skou et al. 2015, Pelletier, Higgins et al. 2015) and the potential for altered pain processing and centrally modulated pain has been recently investigated and discussed in RC tendinopathy (Gwilym, Oag et al. 2011, Littlewood, Malliaras et al. 2013).

Neuroplasticity is the term used to refer to changes in the neuronal properties, structure and organisation of the nervous system in response to new experiences (Latremoliere and Woolf 2009). Neuroplastic changes have been demonstrated in response to experiences and behaviours (Recanzone, Merzenich et al. 1992, Pascual-Leone, Nguyet et al. 1995), motor learning (Bayona, Bitensky et al. 2005, Adkins, Boychuk et al. 2006), pain (Flor 2002, Pelletier, Higgins et al. 2015), injury (Elbert and Rockstroh 2004) and cognitive processes (Lotze and Halsband 2006). Neuroplastic changes are known to change or amplify sensory transmission and this can have functional implications. Sensory testing has demonstrated altered sensory transmission and processing in patellar tendinopathy (van Wilgen, Konopka et al. 2013) and lateral epicondylar tendinopathy (Fernandez-Carnero, Fernandez-de-Las-Penas et al. 2009). These studies found changes in perception thresholds to noxious and innocuous stimuli, evidence of neuroplasticity and central sensitisation.

Central sensation occurs as a result of neuroplasticity (Latremoliere and Woolf 2009) and is an altered pain processing state with increased excitability and synaptic efficiency of the dorsal horn cells in the spinal cord (Gifford 1998). Central sensitisation is thought to occur as a result of significant nociceptor inputs following injury; however it can also persist in the absence of afferent stimulus, which is known as pain memory (Woolf 2011). Central sensitisation manifests itself as pain hypersensitivity and allodynia (the triggering of pain by non-noxious stimuli) (Woolf 2011).

The effect of central sensitisation has been investigated in patients undergoing sub-acromial decompression. Those patients who presented pre operatively with higher levels of central sensitisation and hyperalgesia, as measured by mechanical pain threshold (punctuate stimuli) reported a significantly worse outcome post operatively (Gwilym, Oag et al. 2011).

Whilst the cause of the pain involved in RC remains unknown the integral role that the CNS may play in the pain presentation requires further investigation.

#### **2.1.10 Possible inflammatory mechanisms underpinning rotator cuff tendinopathy**

In relation to this thesis it is the potential inflammatory mechanisms which are of particular relevance. The presence of an inflammatory response in RC tendinopathy forms the theoretical basis for the potential efficacy of the long-chain omega-3 PUFAs in the treatment of this condition.

The involvement of the inflammatory response in the development or continuation of tendinopathy is subject to extensive debate (Longo, Berton et al. 2011). The beginning of 21<sup>st</sup> Century saw a shift from the inflammatory based tendinitis model of the 1970s to a degenerative model without the presence of inflammation and more recently to a model of degeneration alongside a chronic inflammatory response (Abate, Silbernagel et al. 2009, Rees, Stride et al. 2013).

The term 'inflammatory response' encompasses a series of complex biological events which occur in the body as the normal defence response to harmful stimuli (such as damaged cells) through injury and pathogens (Calder 2011, Janssen and Henson 2012). It protects and attempts to heal through the elimination of pathogens and tissue repair processes (Calder, Albers et al. 2009). Inflammation is commonly categorised as either acute or chronic. Acute inflammation is short in duration and is the primary response by the body following injury, concluding with healing (Weiss 2008, Buckley, Gilroy et al. 2013). It is predominated by the infiltration of plasma proteins and leukocytes from the blood into the local area. A cascade of biochemical events allows maturing of the inflammatory response which, if not resolved, leads to a shift in the nature of the cells to chronic inflammation (Janssen and Henson 2012, Buckley, Gilroy et al. 2013).

Chronic inflammation in contrast has been described as;

"A prolonged, dysregulated and maladaptive response that involves active inflammation, tissue destruction and attempts at tissue repair." Weiss (2008) pg 247.

It is characterised by the infiltration of monocytes which differentiate locally into cells such as macrophages and lymphocytes (Maskrey, Megson et al. 2011). It is the process of resolution which is believed to be crucial to the switching off of the inflammatory response (Alessandri, Sousa et al. 2013).

The inflammatory component to RC tendinopathy is evidenced by the presence of inflammatory cells and the molecular mediators of inflammation (Gotoh, Hamada et al. 1997, Matthews, Hand et al. 2006, Millar, Hueber et al. 2010, Gumina, Natalizi et al. 2013).

#### **2.1.10.1 Cellular evidence of inflammation**

A complete absence of inflammatory cells within RC tendinopathy has been reported by histological studies, often descriptive in nature (Jozsa, Balint et al. 1982, Chard, Cawston et al. 1994, Hashimoto, Nobuhara et al. 2003). The use of basic histological techniques in these studies without the use of cell markers has meant that the potential role of inflammation in tendinopathy was overlooked. With the advent of new immune-histochemical techniques (Ramos-Vara 2011) and the increased understanding of the process of chronic inflammation, the role of inflammation in tendinopathy has been revisited (Rees, Stride et al. 2013, Dean, Gettings et al. 2015).

Significantly higher levels of inflammatory cells have been observed in human RC tendinopathy specimens compared to healthy control tendons (Gotoh, Hamada et al. 1997, Matthews, Hand et al. 2006, Millar, Hueber et al. 2010). These three studies have all examined RC tendinopathic tendon in comparison to control groups comprising of cadaver specimens (Gotoh, Hamada et al. 1997) or subscapularis tendons harvested from those undergoing shoulder stabilisation surgery (Matthews, Hand et al. 2006, Millar, Hueber et al. 2010). Two studies described the cellular differences without using statistical tests (Gotoh, Hamada et al. 1998, Matthews, Hand et al. 2006) which may have confounded the findings of the investigations. The final study by Millar et al (2010) investigated RC tendinopathy compared to RC tears and normal control RC tendon using statistical tests to examine the differences between the groups and between the different structural stages of tendinopathy. All three studies observed an increase in the number of macrophages in the RC tendinopathic specimens compared to the healthy controls. This finding supports the potential presence of inflammation in RC tendinopathy.

Macrophages form a critical step in the inflammatory process as they are involved in promoting tissue repair through phagocytosis, the clearing up of damaged cells and the process of resolution (Brecht, Gomez et al. 2008). They also signal the release of cytokines (Cavaillon 1994). In the mouse model, reduction in macrophage concentrations has been shown to increase the tensile strength of healing Achilles tendons (de la Durantaye, Piette et al. 2014).

Two studies observed an increase in mast cells in the tendinopathic RC specimens compared to the healthy control tendons (Matthews, Hand et al. 2006, Millar, Hueber et al. 2010). The importance of increases in mast cell density lies in their key role in the inflammatory process as they release histamine, prostaglandins, leukotrienes, growth factors and proteinases (Kragssnaes, Fredberg et al. 2014). Mast cells have been demonstrated to exert pro-inflammatory effects in human tenocytes in vitro (Behzad, Sharma et al. 2013). The pro-inflammatory effects included; enhanced tenocyte survival

or proliferation, enhanced expression of the enzyme cyclooxygenase (COX)-2 and associated increased production of the inflammatory mediator prostaglandin E<sub>2</sub>, which reduced type I collagen production (Behzad, Sharma et al. 2013). These effects may modulate tendon degeneration and repair and as such, a treatment aimed at inhibiting mast cells may provide beneficial effects in tendinopathy.

#### **2.1.10.2 Molecular evidence of inflammation**

Inflammation comprises many molecular elements (Rees, Stride et al. 2013) but transcription factors and cytokines are the two molecular pathways for which there is evidence to indicate that omega 3s PUFAs might have a beneficial effect. The presence of these molecules within RC tendinopathy further underpins the theoretical basis of this thesis.

##### **2.1.10.2.1 Transcription factors**

Transcription factors are proteins which function in the cell nucleus and are able to control the activity of a gene by governing whether the gene's deoxyribonucleic acid (DNA) is transcribed into ribonucleic acid (RNA) (Gilmore 2006, Whitfield, Wang et al. 2012). Nuclear factor- $\kappa$ B (NF $\kappa$ B) is the primary transcription factor involved in inflammatory signalling pathways (Kumar, Takada et al. 2004, Sigal 2006). It regulates numerous cytokines (including IL-1, IL-2, IL-6, IL-12, TNF $\alpha$ , VEGF), chemokines (including monocyte chemo attractant protein-1), adhesion molecules, E-selectin, inducible nitric oxide synthase (iNOS), growth factors and cyclooxygenase-2 (Ghosh and Karin 2002, Meffert, Chang et al. 2003, Gumina, Natalizi et al. 2013). It has been demonstrated to control anti apoptotic gene expression (Taylor 2008) and contribute to the formation of angiogenesis (Min, Kim et al. 2003).

Gumina et al (2013) investigated the role that NF $\kappa$ B might have to play in the development and healing of RC tears. Samples of RC tendon were excised during surgery in 63 patients who had sustained a non-traumatic tear. Increased levels of activated p65 factor (one of the five transcription factors which make up NF $\kappa$ B) were observed on the margins of the tendon rupture which correlated positively with size of tear. The control tissue used within this study was samples of 'uninjured' subscapularis tissue excised with the supraspinatus tissue; these samples of subscapularis in the majority of samples also showed increased levels of p65 factor and as such cannot be considered as a control. This study used immune-histochemical staining methods and the results would have been usefully further validated by polymerase chain reaction analysis. The association between activated NF $\kappa$ B and RC tendinopathy is an important one and in part based on its ability to regulate inflammatory cytokines.

##### **2.1.10.2.2 Cytokines**

Cytokines are small cell signalling protein molecules which regulate the body's responses to infection, inflammation and trauma (Maffulli, Longo et al. 2011). It is through their role in cell proliferation, differentiation, chemotaxis, apoptosis and



matrix synthesis, that cytokines have the potential to significantly impact RC tendinopathy (Savitskaya, Izaguirre et al. 2011). They are considered vital to the initiation and perpetuation of RC pathology in humans (Millar, Wei et al. 2009).

Cytokines have also been shown to have a direct influence on pain within human musculoskeletal conditions by activating nociceptive sensory neurones (Zhang and An 2007). Pro-inflammatory cytokines (IL-1 $\beta$  and TNF  $\alpha$ ) (Zhang, Li et al. 2002, Ozaktay, Kallakuri et al. 2006, Schaible, von Banchet et al. 2010) are thought to directly modulate neuronal activity in the peripheral and CNS (Zhang and An 2007).

Increased expression of inflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL -33 and tumour necrosis factor  $\alpha$ ), have consistently been observed in patients with RC tendinopathy (Gotoh, Hamada et al. 1997, Sakai, Fujita et al. 2001, Blaine, Kim et al. 2005, Voloshin, Gelinas et al. 2005, Molloy, Kemp et al. 2006, Ko, Wang et al. 2008, Millar, Wei et al. 2009, Blaine, Cote et al. 2011, Savitskaya, Izaguirre et al. 2011, Millar, Gilchrist et al. 2015). It has been suggested that macrophage derived, pro-inflammatory interleukins such as IL- 1 $\beta$  or IL-33 might be an initiator of tendinopathy (Mobasheri and Shakibaei 2013, Millar, Gilchrist et al. 2015) as is seen in osteoarthritis (Wojdasiewicz, Poniatowski et al. 2014).

Increased levels of pro-inflammatory interleukins (IL-1 $\beta$ , IL-1 $\alpha$  and IL-6 ) have also been identified in RC tendon from patients with associated sub-acromial bursitis (Blaine, Cote et al. 2011) and within the subacromial bursa in patients with RC tears. (Voloshin, Gelinas et al. 2005). This involvement of the bursal tissue alongside a RC tear would support co-treatment or systemic treatment to address the bursal reaction as well as the tendinopathy.

Increased levels of systemic pro-inflammatory cytokines (IL-1 $\beta$ , IL6, IL8, IL10, VEGF, bFGF, angiogenin) have been observed in one study in the peripheral blood serum of individuals with RC tendinopathy compared to an age and gender matched control group (Savitskaya, Izaguirre et al. 2011). However the RC group had a higher BMI (1.4kgm<sup>2</sup>) which may have impacted on the levels of circulatory inflammatory cytokines as they have been shown to be raised with increasing adiposity (Harford, Reynolds et al. 2011).

Modification of cytokine expression is an alluring prospect for possible treatment development but as yet has only been preliminarily investigated in the rodent model. The mechanical properties of healing tendon in IL-6 deficient mice were found to be inferior to normal mice (Lin, Cardenas et al. 2006). Also, TNF $\alpha$  blockade has been found to improve the strength of early (second and fourth but not eighth postoperative weeks) tendon to bone healing in rats (Gulotta, Kovacevic et al. 2011).

## Summary

In conclusion, whilst much is still being unravelled about the pathophysiology of RC tendinopathy there does appear to be evidence for an inflammatory component at the cellular and molecular level. The accumulation of inflammatory cells in human tendons (Gotoh, Hamada et al. 1997, Matthews, Hand et al. 2006, Millar, Hueber et al. 2010) and animal model (Andersson, Backman et al. 2011, Pingel, Wienecke et al. 2013) and increased levels of pro inflammatory cytokines in human tendinopathic RC tissue (Sakai, Fujita et al. 2001, Blaine, Kim et al. 2005, Voloshin, Gelinas et al. 2005) and in the animal models (Koshima, Kondo et al. 2007, Millar, Wei et al. 2009, Dohnert, Venancio et al. 2012, Legerlotz, Jones et al. 2013) support this hypothesis.

The pathophysiology of this common disorder is clearly multifactorial and treatment needs to be designed to address different aspects of the pathophysiology. Current treatment options do not achieve optimal outcomes, with one third of patients still presenting with pain and disability after intervention (Seitz, McClure et al. 2011). This thesis is designed to assist in the development of novel treatment options for RC tendinopathy.

The next chapter will discuss the assessment of RC tendinopathy and the non-surgical treatment options which are of relevance to this thesis.

## **Chapter 3 : Rotator cuff tendinopathy.**

### **Assessment & non-surgical management:**

#### **Review of the Literature**

## **Clinical assessment and diagnosis of rotator cuff tendinopathy**

Rotator cuff (RC) tendinopathy is defined as pain and dysfunction of one or more of the deep tendons of the shoulder known as the rotator cuff (supraspinatus, infraspinatus, subscapularis and teres minor). It is characterised by pain, limitation of active range of motion of the shoulder joint and subsequent loss of function (Lewis 2009, Maffulli 2011). The term RC tendinopathy is a clinical classification and relates to the symptoms of pain and loss of function without reference to pathology (Lewis 2009).

Clinical assessment involves a detailed and comprehensive subjective history (including the elimination of causation due to systemic health problems) followed by a combination of impairment measures such as range of movement, strength testing, postural assessment, palpation, special orthopaedic tests, and finally appropriate validated functional disability measurements or patient reported outcome measures (Litaker, Piro et al. 2000). The clinical diagnosis of RC tendinopathy is based on common diagnostic criteria rather than one specific test. However, the presenting clinical features of RC tendinopathy are frequently inconsistent (Via, De Cupis et al. 2013).

### **3.1.1 Subjective history**

The following are features of the subjective history suggestive of RC tendinopathy:

- Symptom duration of more than three months (Littlewood, Ashton et al. 2012).
- Antero-lateral shoulder pain (Gumina, Candela et al. 2014).
- Intermittent shoulder ache (Shin 2011).
- Night pain which can wake the patient from sleep (Litaker, Piro et al. 2000).
- Weakness and/or loss of shoulder function (especially activities involving hand behind back postures and overhead activities) (Shin 2011).
- People older than 40 years (Burbank, Stevenson et al. 2008).
- Functional limitations of the individual in activities relating to different positions of the upper limb (Longo, Berton et al. 2011).

### **3.1.2 Objective assessment**

The following are features of the objective evaluation which support a diagnosis of RC tendinopathy:

- Muscle weakness or atrophy of the RC muscles (Shin 2011).
- Pain on palpation of the peri-articular soft tissue structures of the glenohumeral joint (Mattingly and Mackarey 1996).
- Pain exacerbated through resisted movements, usually external rotation and abduction (Lasbleiz, Quintero et al. 2014).

### 3.1.2.1 Palpation

Tendon palpation is used as part of the clinical examination of RC tendinopathy (Mattingly and Mackarey 1996, McShane, Graveley et al. 2004). The most effective positions to palpate the individual tendons of the RC was examined in 12 cadavers, looking for the point at which the tendons were maximally exposed with the least amount of overlying soft tissue (Mattingly and Mackarey 1996). This study verified that the most effective position for palpating the supraspinatus tendon was that suggested by Cyriax (1993) (maximal shoulder adduction, medial rotation and elbow flexed to 90° in a hand behind back posture) (Cyriax and Cyriax 1993) but with added glenohumeral joint hyperextension. It was noted that in this position however it is difficult to differentiate between the long head of biceps and supraspinatus tendons. The palpation of supraspinatus as part of the assessment of a patient with shoulder pain was also supported by Toprak et al (2012), who examined 69 participants with unilateral shoulder pain of more than six months duration and with no deficit in range of motion and no history of surgery. The positions used to palpate the RC of tendons were not described, making translation of the findings problematic and not allowing comparison to be made with the findings of Mattingly and Mackarey (1996). Palpation of supraspinatus was found to have a higher level of sensitivity (92% [95% CI= 78-95]) than palpation of the other RC tendons and to be superior to both Neer's and Hawkin's Kennedy tests (Toprak, Ustuner et al. 2013). However the specificity of the supraspinatus palpation test was low (41% [95%CI= 18-64]). The reference standard used was ultrasonography. The appropriateness of ultrasonography as a reference test is uncertain as RC tears have been identified in people without symptoms (Tempelhof, Rupp et al. 1999, Yamaguchi, Tetro et al. 2001).

Similarly in a study investigating the clinical features of bursal side partial thickness RC tears 89.5% (34/38) of patients had tenderness of the greater tuberosity on palpation (Xiao, Cui et al. 2010). The position, pressure and method used to palpate the greater tuberosity in this study, however, were not detailed and the study was of poor methodological quality, with inadequate reporting.

Uncertainty exists regarding of the sensitivity of palpation of the greater tuberosity in RC tendinopathy. However palpation is used clinically (Mattingly and Mackarey 1996, McShane, Graveley et al. 2004). Whilst palpation cannot confirm a diagnosis, pain on palpation of the great tuberosity assists in forming a clinical picture implicating the tendons of the RC, and as such palpation formed part of the inclusion criteria.

### 3.1.2.2 Special orthopaedic tests

Special orthopaedic tests aim to assist the diagnosis of RC tendinopathy by stressing potentially pathological structures in order to assess their integrity and function (Biederwolf 2013). They are often used clinically to differentiate between different structures (Biederwolf 2013).

There are 21 clinical tests for RC disorders described in the literature (Longo, Berton et al. 2011). These include; the full can, empty can or Jobe's, Neer's, Hawkins-Kennedy, drop arm, palpation of the supraspinatus, painful arc, resisted muscle tests, Gum-turn, drop-arm, lift-off, bear-hug, belly-press, belly off, Napoleon, drop sign, lag signs and muscle atrophy.

Several systematic reviews including one Cochrane review have been carried out examining the evidence to support diagnostic physical tests for the RC (Hughes, Taylor et al. 2008, Lewis 2009, Hegedus, Goode et al. 2012, Hanchard, Lenza et al. 2013, Hermans, Luime et al. 2013, Somerville, Willits et al. 2014). The overwhelming conclusion of these reviews is that there is no one specific test which is capable of differentially diagnosing RC tendinopathy due to the tests lack of specificity in being able to test one tendon in isolation. Tests have also been described and named in inconsistent ways and with differing positive criteria thereby making it difficult to robustly compare tests (Longo, Berton et al. 2011). There is also great variation in how the tests are performed and interpreted, further complicating the analysis of the given tests (Hanchard, Lenza et al. 2013).

A battery or collection of tests is recommended to improve the clinical accuracy of diagnosis of RC tendinopathy (Somerville, Willits et al. 2014) but their limited value in making a diagnosis of tendinopathy is acknowledged (Hegedus, Goode et al. 2012). When used in combination, if a negative result is obtained using the Neer, Hawkins-Kennedy and empty can tests it has been suggested that a diagnosis of RC tendinopathy can be excluded (van Zuydam, van Rensburg et al. 2015). However, this is not a finding supported by the comprehensive meta-analysis conducted by Hegedus (2012). The low negative likelihood ratios of the Neer (0.47 [95 CI=0.39-0.56]) and Hawkins-Kennedy (0.46 [0.36-0.60]) make it unlikely that a diagnosis of RC tendinopathy could be ruled out if these were negative (Hegedus, Goode et al. 2012).

Uncertainty exists regarding the usefulness of special orthopaedic tests in the diagnosis of RC tendinopathy to definitively confirm which RC tendon is associated with symptoms (Hegedus, Goode et al. 2012). However, these tests are used extensively both in clinical assessment (Hegedus, Goode et al. 2012, Biederwolf 2013) and research investigations (Haahr, Ostergaard et al. 2005, Ketola, Lehtinen et al. 2009, Ketola, Lehtinen et al. 2013) involving the RC. While these special orthopaedic tests (empty and full can, Neer's impingement sign and Hawkins-Kennedy) cannot confirm a diagnosis with certainty, positive findings (pain and / or weakness) they help build a clinical picture that the symptoms are related to the RC tendons, and as such formed part of the inclusion criteria in the RCT.

### **Problems in deriving a definitive diagnosis**

The main difficulty in accurately diagnosing RC tendinopathy is that there is not a gold standard test which can be used as a comparative consistently within both clinical and research fields (Lewis 2009, Somerville, Bryant et al. 2013). Imaging is commonly used as a reference standard with which to compare clinical diagnostic tests (Longo, Berton et al. 2011). However, findings from both magnetic resonance (MRI) and ultrasound (US) images have proven to demonstrate a poor correlation with symptoms and function (Frost, Andersen et al. 1999, Worland, Lee et al. 2003). When comparing MRI

findings in an aged matched symptomatic sub acromial impingement syndrome group versus an asymptomatic group, Frost et al (1999) were unable to distinguish between the two groups based on the structural pathology. Furthermore, up to 40% of the general population and elite overhead athletes have asymptomatic RC tears (Tempelhof, Rupp et al. 1999, Connor, Banks et al. 2003, Worland, Lee et al. 2003, Yamamoto, Takagishi et al. 2010). This presence of full thickness tears in asymptomatic individuals further questions the applicability and usefulness of imaging (Frost, Andersen et al. 1999).

Findings at surgery have been used as the 'gold standard' comparator test however there is a poor level of association between symptoms and structural compromise of the RC (Milgrom, Schaffler et al. 1995, Frost, Andersen et al. 1999, Tempelhof, Rupp et al. 1999) which questions the use of surgical structural findings as a valid reference (Lewis 2009, Lewis 2011).

### **Non-surgical Management of Rotator Cuff tendinopathy**

A wide range of non-surgical treatment options exist for RC tendinopathy. Exercise is increasingly regarded as the optimal treatment option for RC tendinopathy (Lewis, McCreesh et al. 2015) and will be discussed below. Other therapeutic approaches such as; electrotherapy, frictions massage and taping (Pegreff, Paladini et al. 2011, Michaleff and Kamper 2013, Shakeri, Keshavarz et al. 2013, Gebremariam, Hay et al. 2014, Osborne, Gowda et al. 2015), pharmacological approaches and invasive procedures, such as; injections, acupuncture and surgery, are outside the scope of this thesis, but have been discussed elsewhere (Settergren 2013, Toliopoulos, Desmeules et al. 2014, Balasubramaniam, Dissanayake et al. 2015, Louwerens, Veltman et al. 2015).

#### **3.1.3 Exercise and rotator cuff tendinopathy**

Exercise therapy is the main treatment offered by physiotherapists in the management of RC tendinopathy. A number of studies have demonstrated a clear and beneficial effect of a graded and structured exercise programme for patients diagnosed with this condition (Bang and Deyle 2000, Haahr and Andersen 2006, Kuhn 2009, Kukkonen, Joukainen et al. 2014, Littlewood, Malliaras et al. 2014, Littlewood, Bateman et al. 2016). Graded and structured exercise therapy has been demonstrated to have an equivalent effect to both injection therapy and surgery for this condition in the short and long term (one to eight years) (Haahr, Ostergaard et al. 2005, Haahr and Andersen 2006, Ketola, Lehtinen et al. 2009, Ketola, Lehtinen et al. 2013). The requirement for surgery has also been shown to be significantly reduced following a graduated and structured exercise programme (Holmgren, Bjornsson Hallgren et al. 2012, Kuhn, Dunn et al. 2013). The benefits of exercise are wide reaching with improved general health and, when compared to surgery, a reduction in the economic and financial burden of surgery (Lewis 2011, Tashjian 2013, Toliopoulos, Desmeules et al. 2014, Lewis, McCreesh et al. 2015). Surgery also carries risks of post-operative infection and complications (Moosmayer, Lund et al. 2010). A Cochrane review examining surgery for RC tendinopathy published in 2008 concluded that no recommendations could be made regarding the efficacy or the safety of surgery for RC disease (Coghlan, Buchbinder et al. 2008).

Exercise is an overarching term and includes a variety of interventions including strengthening exercises, eccentric, concentric, weight bearing, non-weight bearing, proprioception exercises, flexibility and stretching or range of motion exercises (Kuhn 2009). Various rehabilitation protocols have been advocated by various authors with little consensus within the literature regarding the optimal rehabilitation protocol.

#### **3.1.3.1 What is the most appropriate type of exercise intervention?**

The marked heterogeneity of approaches and types of exercise intervention within the literature makes comparison difficult and the recommendation of one programme or method challenging (Hanratty, McVeigh et al. 2012, Gebremariam, Hay et al. 2014). However the unifying objectives of exercise therapy are; reduction of pain, restoration of function and range of motion, guide the clinical prescription of exercise for RC tendinopathy.

A recent systematic review examined the evidence for loaded exercise (exercise against gravity or resistance) in the treatment of RC tendinopathy (Littlewood, Ashton et al. 2012). Only four studies met the inclusion criteria, one of which investigated a non-clinical population (Ludewig and Borstad 2003). The exercise programmes were applied in different ways, from home exercise to supervised exercise with a physiotherapist, making a definitive comparison difficult. Two of the studies included in that review used a no intervention group as their control group (Ludewig and Borstad 2003, Lombardi, Magri et al. 2008). Without any intervention and no interaction with a therapist the confounding factor of the potentially beneficial patient-therapist relationship is then not controlled for (Littlewood, Ashton et al. 2012). However the results suggest that both supervised and home exercise programmes consisting of loaded exercises might be more effective than no intervention or placebo.

Two studies have investigated the effects of isometric elbow flexion contractions in healthy individuals and concluded that post contractions the pressure pain ratings were decreased and pain threshold was increased (Hoeger Bement, Dicapo et al. 2008, Lemley, Drewek et al. 2014). Due to the lack of an alternative exercise group in either study it is hard to draw conclusions about the reduction in pain being as a result of isometric exercise specifically or exercise in general. Evidence exists that glenohumeral external and internal rotations have opposing effects on subacromial pressure (Werner, Blumenthal et al. 2006), with external rotation lowering pressure. Additionally, exercises to depress the humeral head may also be warranted (Lewis 2009).

In their pilot and later well-designed RCT, Littlewood et al (2014 and 2015) demonstrated that one exercise had equivalent effects on function and pain to usual physiotherapy (a range of interventions including advice, stretching, exercise, manual therapy, massage, strapping, acupuncture, electrotherapy and corticosteroid injection) as measured by the Shoulder Pain and Disability Index (SPADI) at three, six and twelve months. These findings indicate that one appropriately targeted



exercise might provide as much benefit and less burden than several exercises targeting the same structure. This is particularly interesting in the clinical context where exercise adherence is frequently poor (Vermeire, Hearnshaw et al. 2001, Hayden, van Tulder et al. 2005) and any strategy to simplify an exercise programme to make it more achievable is welcomed.

#### **3.1.3.2 Individual or group exercise?**

No evidence or guidance could be found pertaining to the relative efficacy of group exercise versus individualised exercise or one to one treatment in RC tendinopathy. Evidence does exist within the field of low back pain (LBP) suggesting that group exercise is as beneficial as individual treatment in LBP population (Lewis, Hewitt et al. 2005, Kaapa, Frantsi et al. 2006). There are reduced health care costs associated with group exercise when compared to individual treatment (Lewis, Hewitt et al. 2005).

#### **3.1.3.3 Supervised or self-managed programme?**

The findings reported by Littlewood et al (2014 & 2015) also indicate that a self-management programme might be as effective as one to one individualised physiotherapy treatment (Littlewood, Malliaras et al. 2014, Littlewood, Bateman et al. 2016). However, there was no statistically significant reduction in the total number of treatment sessions in the self-managed group when compared to the usual physiotherapy group (Littlewood et al 2015). Whilst not observed in the study by Littlewood, a self-management programme, hypothetically has the potential of being less burdensome in terms of time and healthcare costs.

#### **3.1.3.4 Is the additional of manual therapy to exercise beneficial in the treatment of rotator cuff tendinopathy?**

Manual therapy is defined by the American Academy of Orthopaedic Manual physical Therapists as;

“Any ‘hands-on’ treatment provided by the physical therapist. Treatment may include moving joints in specific directions and at different speeds to regain movement (joint mobilisation and manipulation), muscle stretching, passive movements of the affected body part, or having the patient move the body part against the therapist’s resistance to improve muscle activation and timing. Selected specific soft tissue techniques may also be used to improve the mobility and function of tissue and muscles” (AAOMPT 2008) pg8.

The addition of manual therapy to exercise for RC tendinopathy has been the subject of several systematic reviews (Desmeules, Cote et al. 2003, Camarinos and Marinko 2009, Ho, Sole et al. 2009, Braun, Bularczyk et al. 2013). The conclusion of these reviews are equivocal. Ho et al (2009) concluded that manual therapy did not confer any additional benefit over other interventions. The other three systematic reviews (Desmeules, Cote et al. 2003, Braun, Bularczyk et al. 2013) concluded that there is a trend exists suggesting that manual therapy combined with exercise improves pain in

individuals with RC tendinopathy. The differences between the conclusions of the systematic reviews is likely to be due to the inclusion of a no benefit trial (Çitaker, Taşkıran et al. 2005) and the qualitative analysis using levels of evidence to define treatment effectiveness in the review by Ho et al (2009).

The studies included in the reviews vary in their methodological quality. The lack of blinded assessors (Conroy and Hayes 1998, Bang and Deyle 2000, Çitaker, Taşkıran et al. 2005) or subjects (Bang and Deyle 2000, Çitaker, Taşkıran et al. 2005) (although this is difficult in manual therapy trials) and the lack of concealed allocation (Conroy and Hayes 1998, Bang and Deyle 2000, Çitaker, Taşkıran et al. 2005) introduces a high risk of bias. This makes affirmative conclusions difficult to draw. All the reviews agree, with the current evidence from the studies investigating manual therapy in RC tendinopathy, the heterogeneity of the populations studied, of the interventions and of the outcomes measures used within the trials, again making the drawing of definite conclusions difficult.

The most recent review was conducted as a meta-analysis and included 21 studies (Desjardins-Charbonneau, Roy et al. 2015). A statistically significant decrease in pain (mean difference, 1.0; 95% confidence interval: 0.7, 1.4), as reported on a 10-cm visual analog scale, was observed when manual therapy was given in addition to an exercise programme (n=226). Whether this 1 point difference represents a meaningful difference is debatable as the minimal clinically important difference (MCID) of the 10 point VAS pain scale is 1.4cm (Tashjian, Deloach et al. 2009). The authors of the meta-analysis comment, due to the 1cm mean difference being within the 95% confidence interval, it is possible that manual therapy might have a clinically meaningful effect.

In a trial involving 120 people diagnosed with RC tendinopathy of more than three months duration, 59 received manual therapy and a home exercise programme and 61 received sham ultrasound over a period of 10 weeks. (Bennell, Wee et al. 2010). The combined exercise and manual therapy group achieved significantly improved scores on the SPADI, but only at 22 weeks (the end assessment point) and not at the primary outcome point of 11 weeks. This suggests that any assessment of physiotherapy intervention should be assessed over the longer term.

The type of manual therapy in the reported studies varies and included; mobilisations with movement (MWMs), end of range mobilisations, manual muscle techniques and manipulations. No consensus has been reached on the optimal methods. There is some evidence from a randomised controlled trial (RCT) (Delgado-Gil, Prado-Robles et al. 2015) just published that mobilisations with movement (MWMs) over a period of four sessions improves pain related to movement. This was a well-conducted trial, which builds on previous studies that have used MWMs for the treatment of RC tendinopathy (Ho, Sole et al. 2009, Djordjevic, Vukicevic et al. 2012).

### 3.1.3.5 What is the optimal duration of treatment?

The optimal duration of exercise treatment is unknown. Since the durations of exercise within existing studies differ, any recommendation of an optimal time frame would be problematic (Hanratty, McVeigh et al. 2012, Gebremariam, Hay et al. 2014). However taking those studies which have shown positive outcomes from exercise treatment for RC tendinopathy (Bang and Deyle 2000, Haahr and Andersen 2006, Ketola, Lehtinen et al. 2009, Kuhn 2009, Ketola, Lehtinen et al. 2013, Kukkonen, Joukainen et al. 2014, Littlewood, Malliaras et al. 2014, Littlewood, Bateman et al. 2016) the range of treatment sessions was between four and 19. The median number of sessions was 8.5 [inter quartile range= 6.25-16].

### 3.1.3.6 Summary

Whilst exercise provides the basis for treatment for RC tendinopathy the optimal exercise intervention, duration and mode of administration remains unclear. Exercise commonly results in a reduction in pain and concomitant increase in function but the gains are modest, with the improvements post treatment often just over the threshold of MCID values for the outcomes used (Littlewood, Bateman et al. 2016). Methods to enhance the gains made with exercise would be a valuable way to assist those with RC tendinopathy further.

## **Dietary intervention and rotator cuff tendinopathy**

Consideration of the causative factors of rotator cuff tendinopathy (Chapter 2) highlights the potential role that lifestyle has to play in the development of this common condition. The role of diet is a relatively new consideration in the treatment of tendinopathies, but its inclusion may be important in the holistic and comprehensive management of patients.

Habitual diet appears to have an influence on chronic low grade systemic inflammation (Galland 2010). Current evidence suggests that following a Mediterranean diet (rich in fruit, vegetables, nuts, olive oil and whole grains)(Esposito, Marfella et al. 2004, Centritto, Iacoviello et al. 2009) and consuming long-chain omega-3 polyunsaturated fatty acids (PUFAs) (Lennie, Chung et al. 2005, Clarke, Shipley et al. 2009, Riediger, Othman et al. 2009) and monounsaturated fatty acids (MUFAs) (Basu, Devaraj et al. 2006, Devaraj, Kasim-Karakas et al. 2006, van Dijk, Feskens et al. 2009) is associated with reduced levels of inflammatory markers in serum. Conversely, a diet high in saturated fatty acids (Arya, Isharwal et al. 2006, Margioris 2009), trans fatty acids (Mozaffarian, Katan et al. 2006, Mozaffarian, Aro et al. 2009), and a high omega-6:omega-3 PUFA ratio (Guebre-Egziabher, Rabasa-Lhoret et al. 2008, Olsen, Fenton et al. 2013) from food is associated with increased levels of inflammatory markers.

Inflammatory processes are known to induce oxidative stress (excessive production of free radicals or reactive oxygen species) and reduce cellular antioxidant defence (Khansari, Shakiba et al. 2009). One way in which diet appears to influence tendinopathy is as a result of oxidative stress. Radak et al (2002) reported that mature rats fed a restricted diet (resulting in

a relative reduction of free radicals) demonstrated significantly less tendon degeneration in comparison to rats fed a normal diet (Radak, Takahashi et al. 2002).

#### **3.1.4 Review of previous PUFA dietary interventions in tendinopathies**

To date two studies have investigated the effects of a combined long-chain omega-3, omega-6 PUFA and antioxidant supplement compared to a placebo tablet with differing conclusions.

Mavrogenis et al. (2004) investigated the use of long-chain omega-3 PUFAs and antioxidants in the treatment of tendon disorders in athletes. In this double-blinded study, 40 recreational athletes with a variety of tendon pathologies were randomized to placebo tablets and 16 treatments of ultrasound, or tablets containing essential fatty acids (long-chain omega-3 PUFAs and omega-6 GLA fatty acids) and antioxidants and 16 treatments of ultrasound. After 32 days there was a mean decrease in pain score in 99% of the treatment group and 31% of the control group. Although confidence intervals were not reported, the difference in pain levels was statistically significant ( $P < 0.001$ ) in favour of the experimental group. There was an approximate five-point reduction (on a ten-point scale) in pain (SD approximate 1.0) in the experimental group at one month, and an approximate two-point reduction (SD approximate 1.5) in the placebo group. This study provided a valuable insight into the potential of these compounds in the management of tendon pathology but was at high risk of bias. In this study, 20 subjects were randomized to each group (40 in total), nine subjects were lost to follow-up (three in treatment group and six in placebo group), and final follow-up (subjective pain scores and estimated levels of sports activity) occurred at 32 days. The study group comprised tendon pathologies from different regions of the body including the shoulder, elbow, and knee. There were 12 subjects with a tendon pathology of the shoulder. Ten were diagnosed as having supraspinatus tendinopathy (five per group) and two as having infraspinatus tendinopathy (both in the experimental group). In general, the regional tendon pathologies were not equally distributed between the two groups. No adverse effects were reported by any of the participants in this study. Data analysis was not conducted by an intention-to-treat analysis and non-compliers were excluded from data analysis. Nine subjects were excluded from the analysis due to non-adherence (defined as failure to document test medication taken or training activity carried out in their diary) or 'protocol violation'.

The authors recommend that additional studies are needed to verify their findings further. Additionally, it is not known whether the benefit in the experimental group was due to the individually active substances alone, or to being combined with ultrasound therapy. It is also not known from this study whether the long-chain omega-3 PUFA, or the antioxidants or the combination of both active substances were responsible for the beneficial effect.

Roe et al (2005) investigated the efficacy of the same supplement from the same manufacturer at the same dose (although not for the same duration) as used by Mavrogenis group but in lateral epicondylitis. This was a double-blinded study with

concealed allocation of 60 participants (55 completed) with lateral epicondylitis. The participants were randomised to placebo (unspecified contents other than not containing vitamins or essential fatty acids) or tablets containing the essential fatty acids (omega 3 PUFAs and omega 6 GLA) and antioxidant tablet for eight weeks. Both groups also received eight sessions of trigger point therapy (one per week) and a structured and graded home exercise programme of eccentric exercises, lasting for the whole study period (24 weeks). There were no statistically significant between group differences observed in pain reduction levels at any of the time points ( $p=0.16$  at eight weeks and  $p=0.76$  at 24 weeks). There was a clinically meaningful mean reduction in pain in both groups on a 10cm VAS scale within both groups of 3cm (95%CI=2.5-4) at eight weeks which continued to reduce up to 24 weeks. Maximum grip and pain free grip were statistically significantly higher in the treatment group at baseline but no between group differences were observed at follow up (at eight, 12 or 24 weeks). A within group change from the baseline in grip strength was only observed at 12 and 24 weeks, not at eight. In this study, 30 subjects were randomised to each group (60 in total), five subjects were lost to follow up and it is not reported to which treatment groups they were allocated. Analysis was on a complete case basis and not on an intention to treat principal, and the final follow up was at six months. There was a large variation in the duration of symptoms with those in the treatment group (18 months; SD=22 months) having a mean duration of symptoms twice as long as those in the placebo group (8 months; SD=4 months). The longer duration of symptoms in the treatment group is likely to be accompanied with a poorer prognosis (Feng, Guo et al. 2003). With such inequality in duration of symptoms at the start of treatment between groups it is not possible to draw definitive conclusions from this study.

## Conclusions

The diagnosis of RC tendinopathy is commonly made on the basis of a clinical assessment. It is difficult to make a definitive diagnosis due to the poor level of association between symptoms and structural compromise of the RC on imaging (Milgrom, Schaffler et al. 1995, Frost, Andersen et al. 1999).

Exercise is the mainstay of treatment but affords limited gains (Littlewood, Bateman et al. 2016). Supplementation with long-chain omega-3 PUFAs and antioxidants has been suggested as a possible adjunct to treatment for tendinopathies but existing evidence has reached equivocal findings (Roe, Brox et al. 2000, Mavrogenis, Johannessen et al. 2004).

It is feasible that a novel approach to RC tendinopathy management, a long-chain omega-3 PUFA supplement, promoting resolution to inflammatory processes, may positively influence biochemical mechanisms proposed to underpin RC tendinopathy. The following section will discuss long-chain omega-3 PUFAs and how they may positively influence RC tendinopathy.

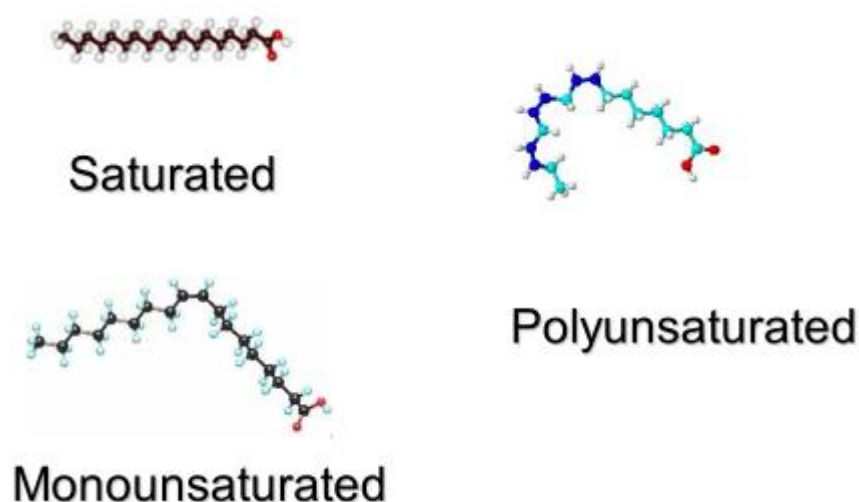
**Chapter 4 : The role of polyunsaturated fatty  
acids & their potential to influence rotator cuff  
tendinopathy: Review of the literature**

## Introduction

In order to consider the mechanisms underpinning a potential association between long-chain omega-3 polyunsaturated fatty acids (PUFA) and rotator cuff (RC) tendinopathy it is necessary to understand the potential mechanisms that PUFAs might impact upon the pathophysiology of RC tendinopathy discussed in the preceding chapters. The section that follows provides background information regarding the history of PUFAs, their chemical family and sources. Their anti-inflammatory mechanism will be discussed as well as the potential role for their use in the treatment of RC tendinopathy.

Dietary fat consists mainly of triacylglycerols which have three fatty acids esterified onto the glycerol backbone (Sanders 2016). There are three main classes of fatty acids: saturated, monounsaturated and polyunsaturated fatty acids (Figure 4.1). Saturated fatty acids are generally straight chain aliphatic hydrocarbon molecules (typically 2-22 carbon atoms long) with a carboxyl group at one end and a methyl group at the other end with each carbon linked by single bonds (Shahidi 2006). As chain length of the saturated fatty acid increases so does the melting point, such that the major dietary saturated fatty acids, palmitic (16:0) and stearic (18:0) acids, are solid at room temperature (Shahidi 2006). Monounsaturated fatty acids are fatty acids containing a single double bond usually 9- carbon atoms from the terminal methyl group (Insel, Turner et al. 2006). The double bonds are normally in the cis-configuration (where the hydrogen atoms adjacent to the double bond are on the same side) this puts a kink in the molecule which has the effect of reducing the melting point such that oleic acid (18:1n-9) has a melting point around 14C° compared with stearic acid which has a melting point of 69 C° (Edelstein 2013). Polyunsaturated fatty acids have two or more double bonds in the molecule and even lower melting points (Sanders 2016).

Figure 4.1 Types of fatty acid



Taken from Sanders TAB (1994) Dietary fats: a briefing paper prepared for the Health Education Authority (with permission) (Sanders and Health Education 1994).

The major dietary polyunsaturated fatty acids are linoleic and linolenic acid and are of plant origin (Sanders 2016). These polyunsaturated fatty acids unlike saturated and monounsaturated fatty acids cannot be synthesis de novo in the body and some are regarded as essential nutrients (Das 2006). This is because mammals lack the necessary enzyme to insert a double bond beyond the seven carbon from the terminal methyl group (Nakamura and Nara 2004). Linoleic acid (18:2n-6) was first discovered to be an essential nutrient and its major metabolite arachidonic acid was shown to be more potent than linoleic at preventing the essential fatty acids deficiency syndrome (Le, Meisel et al. 2009). In the 1960's and 1970's metabolites of arachidonic acid, such as prostaglandins and leukotrienes, were shown to be important signalling molecules involved in the regulation of many physiological functions including inflammation (Funk 2001). PUFAs derived from linoleic acid and its metabolites regulate a broad range of bodily functions including blood clotting, blood pressure, development and functioning of the brain and nervous system. The term eicosanoid is now used to describe oxygenated metabolites derived from 20 carbon polyunsaturated fatty acids (Agarwal, Reddy et al. 2009). For many years alpha linolenic acid (18:3n-3) was regarded as partially essential owing to its ability to correct some but not all of the signs of essential fatty acid deficiency in animals. However, its metabolite docosahexaenoic acid (22:6n-3; DHA), is a major component of the lipid in membranes of the retina and brain and its replacement by the corresponding metabolite, docosapentaenoic acid (22:5n-6), results in impairment in visual function and learning ability (WHO/FAO 2010). Although DHA can be synthesised from linolenic acid, its rate of synthesis may be insufficient in the preterm infant and so needs to be supplied in the diet (Lapillonne and Jensen 2009).

Fish oil is unusual in that it contains high amounts of eicosapentaenoic (20:5n-3; EPA) and docosahexaenoic (22:6n-3; DHA) acids. The fatty acids originate from algae and plankton in the marine food chain and accumulate in marine life up the food chain. The consumption of fish oil containing EPA and DHA, which are often referred to as long-chain long-chain omega-3 fatty acids, exerts a number of pharmacological properties including potentially an anti-inflammatory effect. Some of these effects are thought to result from competition with metabolites from linoleic acid (the omega-6 fatty acids). Linolenic acid found in vegetable oils such as rapeseed and soybean oil can be converted to EPA and DHA (Figure 4.2) albeit slowly (Brenna 2002, Burdge and Calder 2005). However, the consumption of linolenic acid does not appear to have the same anti-inflammatory effects as the preformed EPA and DHA (Calder 2006).

Long-chain omega 3 and Omega 6 PUFAs constitute important structural parts of phospholipid cell membranes which have vital and varied physiological functions (Simopoulos 1999, Burdge and Calder 2005). The makeup of phospholipid cell membranes influences permeability to other molecules or membrane fluidity to assure the correct environment for membrane protein function and lipid raft formation (Yaqoob 2009). Lipid rafts are regions of the phospholipid cell membranes which serve to co-locate proteins involved in intra-cellular signalling (Calder and Yaqoob 2007). Subsequently PUFAs affect the behaviour of membrane bound enzymes, receptors and signal transduction (Wall, Ross et al. 2010).



Importantly in the treatment of RC tendinopathy, PUFAs are also believed to play a role in regulating the inflammatory response (Calder 2006, Das 2006).

Omega-3 PUFAs (also known as n-3 PUFA or  $\omega$ -3 PUFA) have the first double bond at carbon number 3 counting from the methyl end. The major omega-3 PUFAs in the diet are:

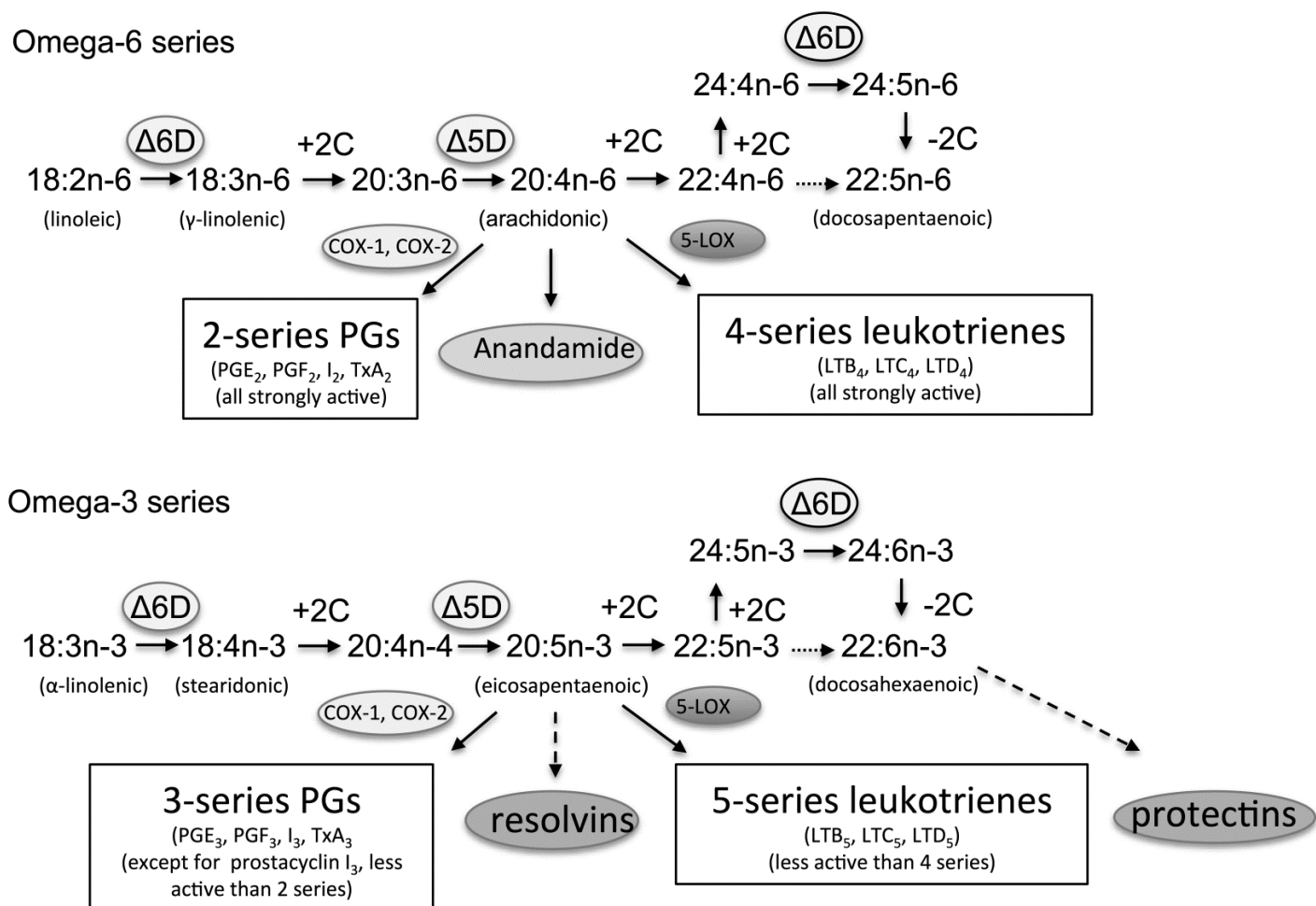
1. Alpha-linolenic acid (18:3n-3; ALA )
2. Docosahexaenoic acid (22:6n-3; DHA)
3. Eicosapentaenoic acid (20:5n-3; EPA)

Omega-6 PUFAs (also known as n-6 or  $\omega$ -6 PUFA) have the first double bond at carbon number 6 counting from the methyl end. The major n-6 PUFAs in the diet are:

1. Linolenic acid (18:2n-6; LA)
2. Gamma-linolenic acid (18:3n-6; GLA)
3. Dihomo-gamma linolenic acid (20:3n-6; DGLA)
4. Arachidonic acid (20:4n-6; ARA)

There is competition between the omega-6 and omega-3 series of fatty acids both for conversion to longer chain metabolites but also in the synthesis of eicosanoids. Generally, the eicosanoids formed from arachidonic acid are biologically active and those from EPA are inactive. However, more recently, novel metabolites called neuroprotectins and resolvins have been identified which may have anti-inflammatory effects (Serhan, Chiang et al. 2008).

Figure 4.2 The essential fatty acids and their metabolites.



Legend:  $\Delta 6D$ ,  $\Delta 6$  desaturase;  $\Delta 5D$ ,  $\Delta 5$  desaturase; COX, cyclo-oxygenase; 5-LOX, 5-lipoxygenase; PG, prostaglandins.

Taken from Sanders TAB (2015) Functional Dietary Lipids, Woodhead Publishing, Kidlington (with permission).

The intake of longchain omega-3 fatty acids is derived mainly from the consumption of oily fish and fish oil supplements. Intakes are negligible in some groups such as vegetarians (Sanders 2014). The United Kingdom (UK) government recommends an intake of two portions of fish a week, one of which should be oily, which would supply approximately 0.45g of longchain omega-3 fatty acids. The intakes of long-chain omega-3 fatty acids from food are typically less than 0.1 g/d. The National Diet and Nutrition Survey (NDNS) results from years 1-4 (combined) of the rolling programme (2008/2009-2011/2012) found that in all age groups the mean intake of oily fish was well below the weekly recommended levels (one portion, 140g/week). In adults aged between 19 and 64 years the mean consumption was found to be 54g per week (men consuming 52g and women 54g) and in the over 65 age groups the mean weekly consumption of oily fish was found to be 90g (103g for men and 81g for women) (Public Health England 2014). However, a significant proportion of the middle-aged and older population reported taking fish oil supplements. Typically commercially purchased fish oils contain

approximately 30-35% long-chain omega 3s, thereby a 1g fish oil capsule would contain 300mg of omega 3 PUFA (Jacobson 2008).

### **Anti-inflammatory properties of n-3 PUFA and mechanisms of action**

PUFAs are believed to influence inflammation via a number of different mechanisms, including;

- PUFA derived eicosanoids (prostaglandins, leukotrienes, resolvins, protectins).
- Down regulated expression of inflammatory cytokine genes- NFκB pathway (Calder 2015).

#### **4.1.1 PUFA derived eicosanoids**

Eicosanoids are pivotal mediators and regulators of the inflammatory response and are derived from 20-carbon PUFAs, largely ARA and EPA (Funk 2001, Tilley, Coffman et al. 2001, Miles and Calder 2012). They include prostaglandins, thromboxanes, leukotrienes and hydroxyeicosatetraenoic acids (Funk 2001). These signalling molecules modulate the intensity and duration of the inflammatory response (Lewis, Austen et al. 1990, Tilley, Coffman et al. 2001). The overall physiological outcome is dependent on the timing of the eicosanoid production, the type of cells present, the nature of inflammatory stimulus and the levels of eicosanoids synthesised (Calder 2008). The phospholipids of neutrophils, lymphocytes and monocytes in those consuming a typical western diet contain 10-20% of ARA, 0.5-1% EPA and 2-4% DHA (Caughey, Mantzioris et al. 1996, Healy, Wallace et al. 2000, Yaqoob, Pala et al. 2000, Kew, Mesa et al. 2004, Rees, Miles et al. 2006). This represents a proportionally high level of ARA in the phospholipid membrane and subsequently ARA becomes the major substrate for eicosanoid synthesis (Calder 2001, Simopoulos 2002). Metabolism of ARA by COX results in the inflammatory 2-series prostaglandins (PG) and the 2 series thromboxanes (Tilley, Coffman et al. 2001, Bagga, Wang et al. 2003). Monocytes and macrophages produce prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and mast cells produce prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) (Kang and Weylandt 2008). Metabolism of ARA by the 5-lipoxygenase (5-LOX) enzyme results in hydroxyl and hydroperoxy derivatives and the 4-series leukotrienes (LT) (Haeggstrom and Funk 2011). With neutrophils, monocytes and macrophages producing leukotriene B<sub>4</sub> (LTB<sub>4</sub>) (Sperling 1998) and mast cells, basophils and eosinophils producing leukotriene C<sub>4</sub> (LTC<sub>4</sub>), leukotriene D<sub>4</sub> (LTD<sub>4</sub>) and leukotriene E<sub>4</sub> (LTE<sub>4</sub>). In general the eicosanoids synthesised from ARA, via cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, are largely ascribed to being pro inflammatory (Bagga, Wang et al. 2003). For example LTB<sub>4</sub> leads to the production of inflammatory cytokines such as tumour necrosis factor alpha (TNFα), interleukin-1beta (IL-1β) and interleukin-6 (IL-6) by macrophages (Tilley, Coffman et al. 2001). The generalisation of all ARA derived eicosanoids being pro inflammatory is recognised as being an over simplification (as Lipoxin A<sub>4</sub> is anti-inflammatory and PGE<sub>2</sub> is known to have both pro and anti-inflammatory effects). However, in excessive concentrations they can contribute to the development of inflammatory disorders (Calder 2009); for example, a common characteristic of rheumatoid arthritis is the excessive production of ARA synthesised eicosanoids (Miles and Calder 2012).

Significant decreases have been observed in the production of PGE<sub>2</sub> and 4 series LT production by human inflammatory cells following supplementation with fish oils over a period of weeks (Caughey, Mantzioris et al. 1996, von Schacky 2004, Rees, Miles et al. 2006).

EPA also acts as a substrate for COX and LOX enzymes but results in the 3-series PGs and TXs (rather than the 2 series), the 5 series LTs, and the hydroxyl-EPA eicosanoids (Kang and Weylandt 2008). The eicosanoids derived from EPA are considered to be less inflammatory or even anti-inflammatory and less biologically active, when compared to eicosanoids synthesised from ARA (Bagga, Wang et al. 2003). A clear demonstration of the difference in potency of inflammatory properties of eicosanoids produced from ARA versus EPA can be seen in the action of LTB<sub>4</sub> versus LTB<sub>5</sub>. EPA derived LTB<sub>5</sub> is 10-100 times less powerful as a neutrophil chemotactic agent than ARA derived LTB<sub>4</sub> and therefore much less inflammatory (Goldman, Pickett et al. 1983, Lee, Mencia-Huerta et al. 1984).

There are two predominant COX isoforms; COX 1 (which is synthesised at a constant rate regardless of the physiological demand or the concentration of substrate) and COX 2 (whose synthesis is increased in response to an inflammatory stimulus (Miles and Calder 2012). In the rabbit model of RC tendinopathy COX-2 expression was found to be stimulated by IL-1 $\beta$  within the torn tendon but also within the articular chondrocytes (Koshima, Kondo et al. 2007). Within humans, Volshin et al (2005) reported that at the time of surgery in 10 individuals with RC tears there was a significant increase in COX 1 and COX 2 in those with RC tears, although this was also observed to a lesser extent in the control group all be it to a lesser extent. However the control group was undergoing shoulder surgery for other shoulder conditions, including; shoulder instability (n = 7) and fracture of the proximal humerus (n = 1) and so raises the question as to whether this was a true control group. Eicosanoids produced by both the COX and LOX pathways (including PGE<sub>2</sub>, leukocytes such as neutrophils and monocytes have been found within the tendon and bursal tissue of individuals with RC tendinopathy (Matthews, Hand et al. 2006).

Non-steroidal anti-inflammatory (NSAIDs) medications are widely used in the management of RC tendinopathy due to their dual effect of anti-inflammatory and analgesic properties.(Pegreff, Paladini et al. 2011). Their use of NSAIDs in RC tendinopathy has been subject to a recent systematic review and meta-analysis (Boudreault, Desmeules et al. 2014). Nineteen trials were reviewed and the authors concluded that in the short term (four weeks) NSAIDs are effective at reducing pain in individuals with RC tendinopathy (Boudreault, Desmeules et al. 2014). NSAIDs were found also to be as effective as corticosteroid injections in the management of pain and reduced function in the short term (Boudreault, Desmeules et al. 2014). NSAIDs are COX inhibitors and their efficacy in RC tendinopathy lends weight to the argument that the COX pathway has an important role to play in the pathogenesis of the condition.

## Summary

With longchain omega-3 PUFA supplementation the availability of ARA for metabolism is reduced as EPA and DHA displace it from membrane phospholipids. This results in fewer inflammatory eicosanoids being produced due in part to the reduced bioavailability of ARA as a substrate. The potential role for the use of long-chain omega-3 PUFA in the treatment of RC tendinopathy is an alluring one and the reduction in inflammatory eicosanoids being produced may in part explain its biological plausibility.

### 4.1.2 Resolvins and protectins

Resolvins (resolution phase interaction products) are potent anti-inflammatory lipid mediators derived directly from EPA and DHA via COX and LOX pathways (Serhan, Hong et al. 2002, Hong, Gronert et al. 2003). EPA is the substrate for E series resolvins and DHA is the substrate for D series resolvins. DHA gives rise to protectins which are similar molecules to resolvins. Resolvins and protectins have been shown to have strong anti-inflammatory and immunoregulatory potential, through the removal of leukocytes and cellular debris (Serhan, Hong et al. 2002, Schwab, Chiang et al. 2007, Serhan, Lu et al. 2007). They have been shown to reduce neutrophil infiltration at sites of inflammation (Serhan, Hong et al. 2002) and regulate and inhibit leukocytes and cytokines thereby decreasing the magnitude of the inflammatory response and possibly aiding its resolution (Serhan, Clish et al. 2000, Janakiram and Rao 2009). For example, resolvin D1 has been shown to inhibit IL-1 $\beta$  and protectin D1 inhibits TNF- $\alpha$  and IL-1 $\beta$  (Serhan, Chiang et al. 2008).

The understanding of the physiology of the resolution to inflammation is still evolving and there is little human research on resolvins or protectins (Miles and Calder 2012, Dakin, Dudhia et al. 2013). The ability to augment or support the resolving processes through the supplementation with EPA and DHA would be very appealing and therapeutically valuable if proven to be effective.

### 4.1.3 Down regulated expression of inflammatory cytokine genes: NF $\kappa$ B pathway

Long-chain omega-3 PUFAs also have the potential to affect inflammation through altered inflammatory gene expression, largely via the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF $\kappa$ B) pathway (Calder 2006). NF $\kappa$ B is the primary transcription factor involved in inflammatory signalling pathways (Kumar, Takada et al. 2004, Sigal 2006). It regulates numerous cytokines (including IL-1, IL-2, IL-6, IL-12, TNF $\alpha$ ), chemokines (including IL-8 and monocyte chemo attractant protein-1), adhesion molecules, E-selectin, inducible nitric oxide synthase (iNOS) and COX-2 (Ghosh and Karin 2002). Several substances and molecules induce NF $\kappa$ B activity including ROS, TNF $\alpha$ , IL-1 $\beta$  and bacterial lipopolysaccharides (LPS), cocaine and ionising radiation (Renard, Zachary et al. 1997, Chandel, Trzyna et al. 2000, Hargrave, Tiangco et al. 2003, Qin, Wilson et al. 2005, Fitzgerald, Meade et al. 2007).

EPA has been demonstrated to block NF $\kappa$ B activity through the reduced degradation of the inhibitory sub unit of NF $\kappa$ B, I $\kappa$ B in cultured pancreatic cells and human monocytes (Lo, Chiu et al. 1999, Novak, Babcock et al. 2003, Zhao, Joshi-Barve et al. 2004).

This is in concordance with the finding that transgenic mice (who endogenously biosynthesise omega-3 PUFA from omega-6 PUFA) were protected from experimental colitis by DHA derived resolvin E1 (Hudert, Weylandt et al. 2006). The authors concluded that the protection from the inflammatory response might be via reduction in NF $\kappa$ B activity and subsequent expression of TNF $\alpha$ , iNOS and IL-1 $\beta$  (Hudert, Weylandt et al. 2006).

LPS or endotoxins, induce an inflammatory response by activating NF $\kappa$ B. EPA and DHA have been demonstrated to inhibit LPS-induced production of inflammatory proteins such as COX-2, iNOS, TNF $\alpha$ , IL-1, IL-6, IL-8 and IL-12 in numerous cell types including endothelial cells (Khalfoun, Thibault et al. 1997), macrophages (Lee, Sohn et al. 2001), monocytes (Babcock, Helton et al. 2004) and dendritic cells (Weatherill, Lee et al. 2005, Kong, Yen et al. 2010). Conversely, saturated fatty acids were found to enhance NF $\kappa$ B activity in macrophages and dendritic cells (Weatherill, Lee et al. 2005).

The generation of IL-1 $\beta$ , IL-6 and TNF $\alpha$  by LPS stimulated macrophages was reduced with a fish oil diet in mice (Yaqoob and Calder 1995). This effect is mirrored in healthy human studies where supplementation with fish oil decreased synthesis of IL-1 $\beta$ , IL-6 and TNF $\alpha$  by LPS stimulated monocytes and lymphocytes (Abbate, Gori et al. 1996, Caughey, Mantzioris et al. 1996, Baumann, Hessel et al. 1999, Trebble, Arden et al. 2003, Ferrucci, Cherubini et al. 2006). However some investigations have failed to show an effect of long-chain omega-3 PUFAs on cytokine concentration (Yaqoob, Pala et al. 2000, Thies, Miles et al. 2001, Kew, Mesa et al. 2004). It is unclear as to the reason for this discordance of results but the reasons may lie in dosage or duration of supplementation with EPA and EHA, technical or methodological factors.

#### **4.1.4 Review of dosage and duration of intake of long-chain omega-3 PUFA used in musculoskeletal conditions**

##### **Dosage of long-chain omega-3 PUFA**

Whether long-chain omega-3 PUFA are capable of producing and the exact doses required to elicit a beneficial or therapeutic effect in musculoskeletal conditions is unknown. The anti-inflammatory effects of long-chain omega-3 PUFA do appear to be dose dependent (Rees, Miles et al. 2006). It has been suggested from human studies in healthy participants that a daily intake of EPA and DHA of 2g or more is required to influence the inflammatory response (Calder 2011). Anti-inflammatory effects of long-chain omega- PUFA have been observed in RA with doses between 2.6g and 7.1g/day (James and Cleland 1997) but not at a dose of 1.0g/day (Geusens, Wouters et al. 1994). However, there is very little literature regarding the dose required to elicit an anti-inflammatory or beneficial response in other musculoskeletal conditions. Table 4.1 details the dose, duration and outcome of studies which have investigated the efficacy of long-chain omega-3 PUFA on musculoskeletal conditions (other than RA). A range from 600mg to 5.1g/day EPA and DHA combined has been used for between one week and 10.5 weeks with little consensus on what dose or time duration is optimal.

There is robust evidence that long-chain omega-3 PUFA have a modest beneficial effect on the symptoms of rheumatoid arthritis (RA) (Fortin, Lew et al. 1995). A recent systematic review on the effects on clinical outcomes of long-chain omega-3 PUFA on RA including 23 studies concluded that there is evidence to support the benefits to joint swelling and pain, duration of morning stiffness, global assessments of pain and disease activity and reduction of NSAIDs use (Miles and Calder 2012). A range of 1.5 to 7g (with a mean of 3.5g/day) EPA and DHA per day has been used in studies on patients with RA (Calder 2008). The authors of a meta-analysis published in 2012 suggested that in RA in order to achieve maximum benefit, supplementation with  $\geq 2.7$ g EPA+DHA and for duration of over three months is optimal (Lee, Bae et al. 2012). In one study investigating the effect of dosage of long-chain omega-3 PUFA on patients with RA, one group (n=20) were provided with a lower dose (27mg/kg EPA + 18mg/kg per day DHA) and one a high dose (n=17) (54mg/kg EPA + 36mg/kg DHA per day) compared to a control group (n=12) taking olive oil, all supplements were taken for 24 weeks. Both doses of EPA and DHA were found to have a similar therapeutic benefit but the higher dose had a shorter period to response. A significant improvement from baseline was observed in the high dose group in the number of tender joints at 18 weeks (p=0.04) and at 24 weeks (p=0.05) (Kremer, Lawrence et al. 1990). Thus indicating that higher doses might elicit a response quicker but with little added benefit otherwise.

The proportion of EPA and DHA in red blood cell membrane lipids increases in a dose dependent manner (Sanders, Hall et al. 2011). The same phenomenon occurs in white blood cells, one study of healthy male volunteers of over 40 years of age, eight participants were randomly assigned to one of six groups (Healy, Wallace et al. 2000). Each group took a different dietary supplement, four of which contained differing concentrations of fish oil (most concentrated was 0.6g EPA plus 1.7g DHA) for 12 weeks. The levels of EPA and DHA were observed to increase in the neutrophil phospholipids in a dose dependent fashion in the groups taking the three most concentrated doses of EPA and DHA.

There does appear to be a 'critical' dose of EPA and DHA certainly in RA. Individuals with RA were given 2.6g/day long-chain omega-3 PUFA or 1.3g/day compared to two placebo groups who were given differing concentrations of olive oil for 12 months (Geusens, Wouters et al. 1994). Only the group taking 2.6g/day long-chain omega-3 PUFA demonstrated significant improvements in a range of outcomes including reduction of pain and anti-rheumatic medication. These findings are supported by those from a dose-response study in healthy volunteers where an EPA intake of 1.4g/day for three months was found to be insufficient to impact ex vivo PGE2 production as compared to an EPA intake of 2.7g/day which was found to significantly decrease PGE2 production (Rees, Miles et al. 2006). These findings would suggest an intake of EPA between 1.4 and 2.7g/day is required to elicit an anti-inflammatory effect.

A dose of 2.6g EPA and DHA (3g long-chain omega-3 fatty acids) was selected for the main randomised controlled trial component investigating the efficacy of long-chain omega-3 PUFAs in the treatment of RC tendinopathy based on the lower predicted efficacy level .



Table 4.1 Doses of long-chain omega-3 PUFAs used in musculoskeletal conditions

Condition	Sample size	Supplement per day	Duration of supplementation	Outcome	Reference
Tendinopathies	Control: 20 (14 completed) PUFA; 20 (17 completed)	3.0g EPA, 2.1g DHA, 2.7g GLA plus100 mg selenium, 15 mg zinc, 1 mg vitamin A, 2.2 mg vitamin B6, 90 mg vitamin C and 15 mg vitamin E	32 days	Decreased pain score in PUFA group of 99% compared to control= 31% (P<0.001), 5 pain reduction on pain VAS in PUFA group vs. 2 point in control	(Mavrogenis, Johannessen et al. 2004)
Lateral epicondylitis	Control: 30 PUFA; 30	3.0g EPA, 2.1g DHA, 2.7mg GLA plus100 mg selenium, 15 mg zinc, 1 mg vitamin A, 2.2 mg vitamin B6, 90 mg vitamin C and 15 mg vitamin E	8 weeks	No between group differences. Both groups improved over 24 month follow up. Significant difference in duration of symptoms at baseline	(Roe, Odegaard et al. 2005)
Muscle soreness post exercise	Control:10 PUFA=10	1.3g EPA +0.3g DHA	6 weeks	No differences between group in muscle soreness but significant reduction in lipid peroxidation and DNA damage in long-chain omega-3 PUFA group.	(Gray, Chappell et al. 2014)
Non-surgical neck or back discogenic pain	250 questionnaires sent , 125 returned	2.4g (EPA + DHA combined) for 2 weeks for 1.2g (EPA +DHA combined) for 4 weeks	75days	59% reported discontinuing NSAIDs, 60% stated improved joint pain, 88% reported continue to take long-chain omega-3 PUFAs	(Maroon and Bost 2006)
Delayed onset muscle soreness following eccentric exercise	Treatment group =69	2.7g (EPA + DHA combined)	30 days	Reduced delayed onset muscle soreness, lower lactate and CRP levels were observed in PUFA group,	(Lembke, Capodice et al. 2014)
Exercise induced inflammation in biceps	11	3.0g (EPA +DHA combined)	7 days	Muscle soreness was 15% less in PUFA group (p=0.004)	Jouris 2011
Moderate-severe Hip and knee osteoarthritis	177	600mg long-chain omega-3PUFA (no ratio of EPA/DHA given) and 1.3g fish oil (no further details given) 1.5g glucosamine sulphate, +vitaminsA,D & E	26 weeks	Pain reduction ≥80% as measured by WOMAC score was statistically significantly better in treatment group.	(Gruenwald, Petzold et al. 2009)

Legend: PUFA= poly unsaturated fatty acid, DHA= docosahexaenoic acid, EPA: eicosapentaenoic acid, GLA= gamma-linolenic acid, VAS= visual analogue scale, DNA= deoxyribonucleic acid, NSAIDs= non-steroidal anti-inflammatory drugs, WOMAC score= Western Ontario and McMaster Universities Osteoarthritis index.

### **Duration of supplementation**

The incorporation of long-chain omega-3 PUFA into the membrane phospholipids of the cells involved in inflammation appears to be time dependent (Browning, Walker et al. 2012). This has implications for the duration of supplementation but also the follow up period where any improvement in a condition might be observed. Yaqoob et al (2000) investigated the effects of taking 3.2g (EPA + DHA) for 12 weeks and plasma phospholipid and peripheral blood mononuclear cell fatty acid composition was examined every four weeks. A maximal effect was observed four weeks after starting supplementation, where there was a 10 fold increase in the proportion of EPA in the plasma phospholipids and a four-fold increase in the peripheral blood mononuclear cell fatty acid composition in the long-chain omega-3 PUFA group. There was also a 20% decrease in the proportion of ARA in the plasma phospholipids and peripheral blood mononuclear cells in the long-chain omega-3 PUFA group during the supplementation period (Yaqoob, Pala et al. 2000).

Similarly, Healy et al (2000) found that the increases in EPA and DHA in the neutrophil phospholipids peaked at four weeks after supplementation with no further increases observed thereafter (Healy, Wallace et al. 2000). This might suggest that an intake of four weeks is sufficient to effect an anti-inflammatory change.

The optimal duration of intake is unknown for the use of PUFA supplements in RC tendinopathy. Previous studies have used a range of intake duration from seven days to 24 weeks in musculoskeletal conditions (see Table 4.1 above).

#### **4.1.5 Review of previous associations/interventions with diet in rotator cuff tendinopathy**

The rationale underpinning marine fish oil supplementation in RC tendinopathy lies in the anti-inflammatory effects of long-chain omega-3 PUFAs. Whilst long-chain omega-3 PUFAs have been found to have some beneficial effects on a range of inflammatory conditions (including, RA, Crohn's disease, Colitis, obesity, chronic obstructive pulmonary disease, asthma, atherosclerosis, neurodegenerative disorders and Type One diabetes) (Calder 2011), it is not possible to directly translate the research carried out in other inflammatory pathologies and other joints (Sanders 2014). However, the up regulation of pro-inflammatory cytokines and eicosanoids is one unifying characteristic of these conditions (Calder, Albers et al. 2009). Whilst their mechanism of action remains under scrutiny there are multiple possible mechanisms by which n-3 PUFAs exert their anti-inflammatory influence including the decreased production of inflammatory cytokines and eicosanoids and increase the production of resolvins and protectins (Calder 2011).

There is consistent evidence indicating the potential benefits of dietary supplementation as an adjunct in the treatment of conditions thought to be associated with, or mediated by inflammatory cytokines and/or oxidative stress (Calder 2001). Two trials of poor methodological quality have reported conflicting findings as to the efficacy of long-chain omega-3 PUFAs for the treatment of tendinopathies (Mavrogenis, Johannessen et al. 2004, Roe, Odegaard et al. 2005). Whilst the potential for dietary supplementation of long-chain omega-3 PUFAs and antioxidants to reduce the disability and morbidity

associated with RC tendinopathy and subacromial bursal pathology is appealing it has not yet been formally investigated (Lewis and Sandford 2009).

## **Conclusions**

Long-chain mega-3 PUFAs have an anti-inflammatory effect, when consumed at adequate doses (Calder 2011). The mechanism by which they have an anti-inflammatory effect is not entirely known but they have the potential to target the inflammatory mediators of RC tendinopathy through a variety of mechanisms including EPA and DHA derived eicosanoids, the increased production of protectins and resolvins and through the down regulation of the inflammatory gene pathways (Calder 2015).

## **Rationale for thesis**

The above review of the literature identifies that there are limitations in the current knowledge base regarding the effect of PUFAs on RC tendinopathy. This is a very new area of research and only a few dietary supplementation trials have been conducted on tendinopathies. Many have not been placebo-controlled or double blinded, or have been under powered (too small a sample size) to detect a change in the selected outcomes. Furthermore they have been at risk of bias with data not analysed on an intention to treat basis.

Due to the uncertainty in the evidence, this thesis sets out to address a number of these issues.

## **Aims and objectives of thesis**

1. To investigate the extent of the current use of dietary supplements in a cohort of individuals with shoulder pain.
2. To explore the reasons for or for not taking supplements and any associations.
3. To conduct a double blinded RCT to evaluate the efficacy of exercise and PUFA in the treatment of RC tendinopathy.
4. To conduct a qualitative study to investigate issues around adherence to carrying out an exercise programme for RC tendinopathy and taking the dietary supplements provided within the RCT.

## **Chapter 5 : Methods**

## **Introduction**

As outlined in Chapter one, the aim of this thesis was to establish the effectiveness of long-chain omega-3 PUFA in the treatment of rotator cuff (RC) tendinopathy. To achieve this, this research investigation involved four interrelated studies;

1. Reliability study investigating the intra and inter-rater reliability of shoulder range of motion and strength (Chapter 6).
2. Survey of shoulder pain and the use of nutritional supplements: a questionnaire based investigation (Chapter 7).
3. A double blind randomised controlled trial investigating the efficacy of long-chain omega-3 polyunsaturated fatty acids and exercise in the treatment of RC tendinopathy (Chapter 8).
4. Exploring experiences, barriers, motivators and enablers to nutritional supplement use and exercise in rotator RC tendinopathy (Chapter 9).

This chapter will describe the methods used in these investigations, including; outcome measures, data collection, power calculations and statistical analyses.

## **Outcome measures**

Health related outcome measures are tools used to evaluate the extent to which healthcare objectives have been achieved, as well as measuring health status and health related quality of life, and impact of a disease or condition (Garratt, Schmidt et al. 2002, Haywood 2006).

Health related outcome measures are important throughout the spectrum of health care provision; from the individual patient and clinician evaluating the effectiveness and efficacy of treatment and progress, to political (e.g. United Kingdom Department of Health) and other health funding bodies (e.g. NHS Clinical Commissioning Groups) assessing the benefit of care in relation to cost. In research, health related outcome measures allow the comparison of different treatments for a specific population of patients. The selection of any health related outcome measurement tool is dependent on the question that is being asked and its context (Cano and Hobart 2011).

Outcome measures need to be valid and reliable with a known minimum error, easily accessible to patients and healthcare professionals with minimal responder or clinician burden and applicable or relevant to the patient group being examined (Collins and Roos 2012). The validity of an instrument is its ability to measure what it purports to measure (Velentgas, Dreyer et al. 2013). The reliability refers to the instruments ability to record the same outcome in the same conditions over time (Velentgas, Dreyer et al. 2013).

The minimally clinically important difference (MCID, also known as the minimally clinically important change MCIC) is the smallest change in an outcome measure that would equate to an important change to the patient (McGlothlin and Lewis

2014). The minimal detectable change (MDC) is the smallest change that can be detected beyond error (Kovacs, Abaira et al. 2008). It is recognised that no single outcome measure can appropriately measure all aspects and the impact of a condition on a patient's life (Porter 2010). The World Health Organisation (2002) international classification stated that a patient's health condition was dependent on; body function and structure, activity and participation and thus a battery or combination of outcome measures should be used to cover these factors.

It has been argued there is need for agreement on core outcome sets appropriate for specific areas (such as musculoskeletal research conducted on the shoulder) so that the findings of investigations may be accurately compared (Gargon, Gurung et al. 2014, Page, McKenzie et al. 2015). Currently there is no core outcome set for the shoulder. There are several widely used condition specific outcome questionnaires but with little agreement as to which are the most responsive for RC tendinopathy.

Disability and impairment are interlinked but are measured in different ways in the context of their definition. Impairment is defined by the American Medical Association (AMA) as "significant deviation, loss, or loss of use of any body structure or body function in an individual with a health condition or disease" and disability as "activity imitations and/or participation restrictions in an individual with a health condition, disorder or disease" (Rondinelli 2008). Impairment measures include methods such as goniometry to measure loss of range of motion. Disability and functional measures include disease specific measures such as the Oxford Shoulder Score (Dawson, Fitzpatrick et al. 1998, Dawson, Rogers et al. 2009) used within this thesis for the measurement of the extent of disability or functional limitation.

Table 5.1 Outcome measures used within each chapter of the thesis.

Chapter	Outcome measures used
<b>Chapter 6:</b> Reliability study: the intra- and inter-rater reliability of shoulder range of motion and strength.	<ul style="list-style-type: none"> <li>• Impairment measure: range of motion of the shoulder using an inclinometer</li> <li>• Impairment measure : strength measurement of the shoulder using the JTECH power II commander</li> </ul>
<b>Chapter 7:</b> Shoulder pain and the use of nutritional supplements; A questionnaire based investigation.	<ul style="list-style-type: none"> <li>• Oxford Shoulder Score (OSS)</li> <li>• Shoulder Pain And Disability Index (SPADI )</li> <li>• Short Form 36 (SF 36)</li> <li>• Euro QoL 5D 3L (EQ5D 3L)</li> </ul>

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**Chapter 8:** A randomised controlled trial of long-chain polyunsaturated fatty acids in the treatment of RC tendinopathy.

- OSS
- SPADI
- SF36
- EQ5D 3L
- Numerical rating score of pain
- Patient specific functional score (PSFS)
- Global impression of change
- Shoulder range of motion
- Strength assessment of shoulder
- Adherence indices; fatty acid composition in blood plasma, capsule count, recorded capsule count.
- Four-day food diaries.

**Chapter 9:** Exploring experiences, barriers, motivators and enablers to nutritional supplement use and exercise in RC tendinopathy: A qualitative study.

Qualitative interviews

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#### 5.1.1.1 Measurement of range of motion

Measurement of physiological shoulder movement is an important part of the clinical examination of a patient with RC tendinopathy. The physiological movements that are most commonly measured include shoulder flexion, abduction, external rotation and the movement of placing the hand behind back (Ginn, Herbert et al. 1997, Alvarez, Litchfield et al. 2005, Lewis, Green et al. 2005, Lewis, Wright et al. 2005). Being able to place your hand behind your back is essential for normal and routine function in activities of daily living such as; tucking in a shirt, reaching for something in a back pocket, attending to personal hygiene, and for women, closing and opening a bra. These functional activities are commonly described by people with RC tendinopathy as activities that are associated with significant pain and restriction in movement and function. Subsequently measurement of range of motion is recommended by both the Society of American Shoulder and Elbow Surgeons and the American Academy of Orthopaedic Surgeons (Kumar and Satku 1994). Within the literature a variety of methods have been used to clinically measure shoulder range of movement (ROM) including, tape measurements, goniometry, inclinometers, visual estimation, digital devices and photography (Kessel 1982, Riddle, Rothstein et al. 1987, Williams and Callaghan 1990, Croft, Pope et al. 1994, Kumar and Satku 1994, Youdas, Carey et al. 1994, Trombly 1995, Green, Buchbinder et al. 1998, Hayes, Walton et al. 2001, Reese and Bandy 2002, Ellenbecker 2004). The positions for the measurement of ROM have not been standardised and several positions have been documented



including sitting in a chair with support (Trombly 1995), in a chair without support, lying supine, side lying, lying prone and in standing (Clarkson 2000, Reese and Bandy 2002, Ellenbecker 2004). The point at which measurements are made has also lacked consistency with measurements being made of shoulder active range, passive range and range to the first point of pain (Green, Forbes et al. 1998, de Winter, Heemskerk et al. 2004, van de Pol, van Trijffel et al. 2010).

Clinically, either visual estimation or goniometry, are commonly used to measure shoulder range of motion. However, the reliability of these methods is uncertain (Croft, Pope et al. 1994, Terwee, de Winter et al. 2005). Valentine and Lewis (2006) examined the intra-observer reliability, in participants with shoulder pain and asymptomatic individuals, of measuring the physiologic movements of shoulder; flexion, abduction in the plane of the scapula, external rotation with the arm by the side, and internal rotation. The authors found that following their measurement protocol the majority of the main physiologic movements of the shoulder were measured with good to excellent intra-tester reliability (Valentine and Lewis 2006). At the time of current thesis trial design, the methodology reported by these authors had the best proven reliability of all methods (Hayes, Walton et al. 2001, Edwards, Bostick et al. 2002) of range of motion measurement of the shoulder in the target population and therefore was used within the study for investigation of reliability and use in the main clinical investigation.

#### **5.1.1.2 Measurement of strength**

The evaluation of shoulder flexion, abduction, internal and external rotation strength, the full and empty can tests (also known as Jobe's test) (Jobe and Moynes 1982, Itoi, Kido et al. 1999) as well as the strength of elbow flexion (as a result of the multi-joint function of the biceps brachii), are routinely performed as part of an examination of shoulder function. Clinically, if available, the strength of the symptomatic shoulder is usually compared to the asymptomatic side. Muscle strength testing using hand held dynamometers (HHDs) has been shown to exhibit good-to-excellent reliability (Hayes, Walton et al. 2002, Bohannon 2005, Kolber and Cleland 2005, Tyler, Nahow et al. 2005) and may be more sensitive for detecting deficits in shoulder external rotation strength than isokinetic devices (Tyler, Nahow et al. 2005). Findings from the reliability study (Chapter 6) indicated that the hand-held JTech PowerTrack™ II Commander HHD (JTECH Medical, Salt Lake City, UT, USA) demonstrated good to excellent intra- and inter-tester reliability for the measurement of asymptomatic shoulder strength (Dollings, Sandford et al. 2011). The mean of three tests was found to produce more reliable measurements than just one measurement (Dollings, Sandford et al. 2011). These findings support those of other reliability trials' investigations for testing shoulder strength using hand-held dynamometers (Agre, Magness et al. 1987, Leggin, Neuman et al. 1996, Balogun, Powett et al. 1998, Hayes, Walton et al. 2002, Vermeulen, Bock et al. 2005). However as a result of different devices being tested using different research protocols, extrapolating the findings between studies is difficult.

## Summary

The assessment method used for measuring strength and shoulder range of motion demonstrated good to excellent reliability for intra-rater reliability re-assessment by both examiners and inter-rater reliability between examiners (Chapter 6) and subsequently these methods were employed in the randomised control trial (Chapter 8).

### 5.1.2 Patient reported outcome measures-used in Chapters 6, 7 and 8

Significant emotional impact from the functional and social limitations and pain experienced with RC tendinopathy has been reported (Minns Lowe, Moser et al. 2014). It is therefore important that these areas are assessed in any outcome measurement tool.

#### 5.1.2.1 Disease specific self-reported disability

##### 5.1.2.1.1 Oxford Shoulder Score (OSS)

The Oxford Shoulder Score (OSS) (Appendix 11.1) (Dawson, Fitzpatrick et al. 1998, Dawson, Rogers et al. 2009) consists of twelve questions, four pertaining to pain (33% of total score) and eight (67% of total score) to assess activities involved in daily function. The OSS was originally scored out of 60 (each item was marked 1-5 with 1 equating to no pain or no functional limitation) and the best score was 12 (Dawson, Fitzpatrick et al. 1998). A revised scoring system was suggested in 2009 in response to criticism that the original scoring system was counterintuitive and causing confusion (Dawson, Rogers et al. 2009). In the revised version each item is rated on a five part Likert scale where 0 is the worst and 4 the best so that a score of 0 equates to maximal disability and 48 to no disability (Dawson, Rogers et al. 2009). The questionnaire asks the respondent to recall symptoms over the past four weeks. The tool takes two to four minutes to complete by the respondent. The OSS has been demonstrated to be responsive in RC tendinopathy and surgery (Dawson, Hill et al. 2002, Ekeberg, Bautz-Holter et al. 2008, Allom, Colegate-Stone et al. 2009).

The OSS has been shown to display both good internal consistency (the correlation between different items that propose to measure similar constructs (Barker, Pistrang et al. 2002)) Cronbach's  $\alpha=0.94$ , and test-retest reliability (the examination of consistency over time (Barker, Pistrang et al. 2002)) Pearson coefficient= 0.98 (Huber, Hofstaetter et al. 2004). The test re-test reliability of the OSS has been examined in participants with subacromial impingement (Cloke, Lynn et al. 2005) and RC tendinopathy (Ekeberg, Bautz-Holter et al. 2008).

Recently, the smallest detectable change and MCIC of the OSS has been found to be 5 and 6 respectively (Ekeberg, Bautz-Holter et al. 2010, van Kampen, Willems et al. 2013).

The OSS was developed as a post-operative tool and there is little existing evidence of its psychometric properties with patients undergoing non-surgical management (Bot, Terwee et al. 2004, Roy, MacDermid et al. 2009, Angst, Schwyzer et al. 2011).

#### **5.1.2.1.2 Shoulder Pain and Disability Index (SPADI)**

The Shoulder Pain and Disability Index (SPADI) (Appendix 11.2) is a 130 point, 13 item self-administered questionnaire covering two domains, pain (five items) and function (eight items)(Roach, Budiman-Mak et al. 1991). Each question is scored on a numerical rating scale with 0 representing 'no pain or no difficulty' and 10 'worst pain imaginable or so difficult it required help. Each question is weighted equally within the domain and each domain carries equal weighting in the overall score which is expressed as a percentage, where 100% represents maximum pain and disability. The questions pertaining to the domain of pain require the respondent to recall pain relating to specific defined activities that captures information not sought on other shoulder specific questionnaires. The SPADI requires the respondent to recall their symptoms over the past week unlike the OSS which asks for recall over the preceding 4 weeks. It takes approximately two minutes to complete and so the burden on the respondent is low, it is also easy and quick to score (Angst, Schwyzer et al. 2011).

The MCIC for the SPADI has been reported to be 8 (Schmitt and Di Fabio 2004), 10 (Paul, Lewis et al. 2004), 13.8 (Williams, Holleman et al. 1995) and 20 points (Ekeberg, Bautz-Holter et al. 2010). The SPADI has been demonstrated to be responsive to change and be able to discriminate between those who are improving and those who are not (Williams, Holleman et al. 1995).

The OSS was originally designed to be a primary outcome measure in randomised controlled trials (Dawson, Rogers et al. 2009) and has been used in a UK nationwide RC trial (UKUFF trial) (Carr, Rees et al. 2014). Despite some of the limitations of the OSS it is widely used as a research and clinical outcome tool throughout the UK and in a survey of 217 NHS shoulder surgeons 69% reported using the OSS as their preferred outcome (Varghese, Lamb et al. 2014). It was due to this clinical utility, its use in the large UKUFF trial and the information available at the time of the design of the study that the OSS was selected as the primary outcome measure.

The primary outcome point within the main study was following the two months of intervention. The next outcome point was one month later (three months from baseline). The SPADI was selected as an outcome in the main study to capture any change between two and three months in particular as it asks the participant to recall the symptoms in the last week rather than the preceding month.

#### 5.1.2.2 Measurement of self-reported pain

Pain associated with RC tendinopathy is often chronic in nature and as such, has a substantial impact on the individual, including their physical, emotional and cognitive function, as well as their productivity, ability to work and earn an income as well as detrimentally impacting on social function (Minns Lowe, Moser et al. 2014). Recall of pain is difficult with the memory of pain often influenced by contextual factors and this makes the accurate measurement of pain problematic (Wiech and Tracey 2009).

Pain is commonly recognised as a key feature in the spectrum of pathology of RC tendinopathy and was listed by people diagnosed with pain associated with supraspinatus tendinitis as their predominant symptom (Nyman, Palenius et al. 2012). Therefore the valid and reliable measurement of pain is essential when considering and comparing the effectiveness of intervention across two groups and carrying out any shoulder assessment. However, as the nature of pain is subjective, personal and private, objective assessment of this domain is difficult (Breivik, Borchgrevink et al. 2008).

The very nature of pain makes its objective measurement impossible (Breivik, Borchgrevink et al. 2008). Clinically the most commonly used tools to assess the intensity of pain are the Visual Analogue Scale (VAS) and the Numerical Rating Scale (NRS). These are one dimensional tools which have been shown to assess pain reliably both at rest and during function (Ferreira-Valente, Pais-Ribeiro et al. 2011). The VAS and NRS have been reported to correlate well in the assessment of the intensity of pain (Ferreira-Valente, Pais-Ribeiro et al. 2011). They are best used to rate the intensity of pain immediately, although they can be used for worst, least or average pain score recall over a period of a week (Singer, Kowalska et al. 2001, Breivik, Borchgrevink et al. 2008). However, the NRS is preferable over the VAS as it is more practical to administer as there is no requirement for pen or paper and appears to be easier to comprehend for most people (Breivik, Borchgrevink et al. 2008).

The NRS is an 11 point scale anchored on the left with 0 representing no pain and 10 as the worst pain imaginable on the right. It has been shown to be reliable and valid within the shoulder (Mintken, Glynn et al. 2009). It is the most responsive commonly used pain measure and is able to detect gender difference in pain intensity (Ferreira-Valente, Pais-Ribeiro et al. 2011). The minimally clinically important difference has been established for the NRS in a cohort of patients with shoulder pain (Mintken, Glynn et al. 2009). Participants referred with shoulder pain to an out-patient physiotherapy clinic completed a quick DASH and NRS at their baseline visit. They then repeated them along with rating their global impression of change two to four weeks later following physiotherapy treatment. The MCID for shoulder pain on movement measured on the numerical rating scale NRS scale was found to be 1.1 points (Mintken, Glynn et al. 2009). The percentage changes in pain intensity has been classified with a 10-20% decrease equating to a minimally important change, 30% to a moderately important change and 50% signifying a substantial improvement (Dworkin, Turk et al. 2008).

The initiatives on methods, measurement and pain assessment in clinical trials (IMMPACT), recommends the use of the NRS and the number of analgesics being taken to measure pain intensity in clinical trials (Dworkin, Turk et al. 2005). On this basis and the practicality of its use the NRS (Appendix 11.18) was selected along with the SF 36 pain sub-scale (discussed below, Appendix 11.3) to measure self-reported pain within the RCT.

#### **5.1.2.3 Health related quality of life**

Generic patient rated outcome measures such as the Short Form (SF) 36 (Ware and Sherbourne 1992) evaluate the broader aspects of a participants' health. Normative data is available allowing comparison with responses from a population of people without shoulder symptoms (Fitzpatrick, Davey et al. 1998). Due to the multidimensional nature of health related quality of life measures they can reveal unanticipated side effects of treatment that region specific outcome measure may miss (Guyatt, King et al. 1999, Wiebe, Guyatt et al. 2003).

These broader quality of life measures were included due to their ability to provide more generalised health information. Chronic pain is recognised to have an impact on physical, emotional and social functions and as such important to measure. Another reason for selecting the SF 36 was its ability to capture this information (Bergman, Jacobsson et al. 2004). It was also determined to be important to include both region specific and more global quality of life measures in order to evaluate comprehensively any change during the trial, as a study comparing the validity of five shoulder questionnaires commented that whilst these shoulder specific questionnaires gave a measure of severity it did not give an indication of overall health (Beaton and Richards 1996).

##### **5.1.2.3.1 Medical Outcomes Study 36- item short form (SF-36)**

The SF 36 is a 36 item questionnaire which is grouped into eight domains, scaled from 0-100, with a higher score representing better health. The domains either physically or emotionally focused and include; physical functioning (PF), role limitations due to physical health (RP), role limitations due to emotional health (RE), energy and fatigue (vitality) (VT), emotional well-being (MH), social functioning (SF), bodily pain (BP) and general health (GH). There are also two summary measures, physical component summary (PF, RP, BP, GH) and the mental health component summary score (VT, SF, RE, MH).

The SF 36 is the most commonly used measure of generic health status in health care research (Ware and Sherbourne 1992, Garratt, Schmidt et al. 2002). It is frequently used as an outcome measure in the field of RC research allowing comparison between studies (Ware and Sherbourne 1992, Bennell, Wee et al. 2010). It can be self-administered or with assistance, on paper or online. It takes approximately five to thirty minutes to complete and is quick to score using on line tools (<http://www.sf-36.org/demos/SF-36.html>).

The EQ 5D 3L (or EuroQol, Appendix 11.4), like the SF 36, is a generic preference-based tool for the measurement of self-reported health-related quality of life (Brooks 1996), and is comprised of two components. The first of which evaluates five dimensions: mobility, self-care, activity, pain and depression and anxiety (evaluated together). Each dimension can be scored as one of three levels, no impairment, mild to moderate impairment and severe impairment. The scores are scaled from -0.04 (worse than death) to 1.00 (perfect health). The second component of the EQ 5D 3L is the EQ VAS (visual analogue scale) where participants are asked to rate their health status a scale from 0 to 100 where 0 represents 'worst imaginable health' and 100 'best imaginable health'.

During the period the main RCT was running, the EQ 5D 3L was replaced by the EQ 5D 5L due to problems with the 3L version delineating small but important clinical changes in health status and the presence of a ceiling effect (when a measure has a distinct upper limit for potential responses and a large number of respondents score at or near the upper limit (Pickard, De Leon et al. 2007, Janssen, Pickard et al. 2013, Lim, Harris et al. 2015). The 5L version differs from the 3L in that there are five levels (no problem, slight problem, moderate problem, severe problem and extreme problem) within each dimension rather than three (Obradovic, Lal et al. 2013). The EQ 5D 5L was not available at the time of the start of the current investigation as because of this the EQ 5D 3L was used.

The EQ 5D 3L has demonstrated good test re test reliability (van Agt, Essink-Bot et al. 1994). It is quick to complete and score. It is commonly included in other trials investigating RC tendinopathy (Odenbring, Wagner et al. 2008, Hultenheim Klintberg, Karlsson et al. 2011, Krischak, Gebhard et al. 2013) and allows an effective measure of general health status (Coretti, Ruggeri et al. 2014).

#### **5.1.2.4 Restoration of functional activity**

The measures of restoration of functional activity were only used in Chapter 8.

##### **5.1.2.4.1 Patient specific functional score**

The Patient Specific Functional Score (PSFS) is a questionnaire that is used to quantify and measure an individual's key activity limitations (Sterling and Brentnall 2007, Horn, Jennings et al. 2012, Nicholas, Hefford et al. 2012) (Appendix 11.5). The participant selects three activities, movements or posture that is causing concern or difficulty in relation to their shoulder problem. It is possible that these activities might not be included on one of the standardised questionnaires (OSS, SPADI). Due to the self-generating nature of the items selected will commonly differ from individual to individual and are therefore not necessarily comparable across individuals (Jolles, Buchbinder et al. 2005). However, it is this individualised nature that allows the PSFS to capture an individual's change in function that might not be identified on the self-reported function measure the OSS, the primary outcome measure in the RCT. The questions should be tailored so that they are pertinent and meaningful to the individual but this does require more involvement from the participant as they have to

self-generate the activity in question and prioritisation of which functions are more problematic for them and thus warrant inclusion. It has been recommended that participants are assisted in the process of using the PSFS and completion of this tool may be a collaborative effort (Stratford, Gill et al. 1995)

The PSFS has been validated for other musculoskeletal conditions including low back pain and the upper extremity (Maughan and Lewis 2010, Hefford, Abbott et al. 2012) but not yet specifically the shoulder. The PSFS has demonstrated moderate to excellent reliability, validity and sensitivity to change and it has recently been shown to be able to be capable of assessment of group level change and between group discrimination in group level data (Abbott and Schmitt 2014).

The MID for the PSFS (on a scale from 0 to 10) ranged from 1.3 (small change) to 2.3 (medium change) to 2.7 (large change) (Abbott and Schmitt 2014). A large study of 1708 patients with a range of musculoskeletal disorders were recruited from physiotherapy clinics and their physical function was assessed at baseline and on discharge, using the PSFS, region specific outcomes and the global rating of change (Abbott and Schmitt 2014). The PSFS was found to perform better than the comparison measures in most categories. The concurrent, convergent and discriminate validities, the scale consistency, distribution and responsiveness of the PSFS were supported by the results and found for both between group discrimination and within-groups assessment of change over time (Abbott and Schmitt 2014).

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#### **5.1.2.5 Global rating of change**

The global rating of change (GROC) was again only used in Chapter 8. The examiner asked participants at two, three, six and 12 months “How much do you feel you have improved or worsened from your first day in the study?” Participants were asked to rate their improvement or deterioration on a Likert scale as a percentage, with 100% equating to full improvement. The global rating of change is often used to evaluate if a patient or participant perceives a change in their symptoms during treatment from baseline. As such, it can be used to divide participants into responders and non-responders (Copay, Subach et al. 2007). The GROC score is quick to complete and poses little respondent burden. However, as it is a one item summary score it is unlikely to be able to detect subtle changes and is subject to influence from current general health, state of mind and expectations from treatment (Fitzpatrick, Davey et al. 1998, Kamper, Maher et al. 2009).

#### **5.1.3 Anthropometric measurements**

Anthropological measurements were taken only in Chapter 8 and refer to the measurement of humans. Within the RCT the anthropometric data collected included the participant’s height, weight and waist circumference.

The height and weight measurements were taken in the clinical ward and the waist circumference in the assessment room both of which were located in the clinical research facility at St. Thomas’s Hospital, London, UK.

#### **5.1.3.1 Height**

Height was measured using a wall mounted manual stadiometer (SECA, Brimingham, UK). The participant was asked to remove their shoes and the investigator ensured that they were standing upright with their heels and shoulders against the measuring rod, their knees and back straight and looking straight ahead. The measuring slide was then pushed down onto the head, compressing the hair, but not bending the measuring slide. The reading was recorded to the nearest 0.1cm.

#### **5.1.3.2 Weight**

Weight was measured on calibrated digital scales (SECA, Birmingham, UK) which were accurate to 0.1kg. Participants were asked to remove their shoes and any outdoor clothing but to remain in light clothing as it was an open ward environment. They then stepped onto the scales and stood upright and still whilst the measurement was being taken. The reading was recorded to the nearest 0.1kg.

#### **5.1.3.3 Waist circumference**

Waist circumference was measured in standing as the mid-point between the lowest rib and the iliac crest (Mason and Katzmarzyk 2009). The measurement was taken just prior to the physical examination whilst the participant was undressed and at the end of expiration using a non-stretch measuring tape placed onto the skin. Care was taken to ensure the tape was placed horizontally and flat. The reading was recorded to the nearest 0.1cm.

#### **5.1.4 Fatty acid analysis within plasma samples blood samples**

The fatty acid composition of the total plasma lipid was measured within this study as opposed to the specific phospholipid class. The measurement of the total plasma lipid determines nonesterified and esterified fatty acid species as a sum (Lepage and Roy 1986). The reason chosen to determine the fatty acid composition of the total plasma lipid was due to fatty acid intake becoming distributed throughout all plasma lipid classes (phospholipid, triacylglycerols, diacylglycerols, monoacylglycerols, non-esterified fatty acids) in a complex way highlighting the problematic approach of selecting a particular class as the most reflective of dietary intake. Use of total lipid fatty acid determination is simpler from a biochemical standpoint and yet allows demonstration of incorporation of the consumed fatty acid and hence adherence of supplement intake without having to consider interactions between various lipid classes (Lepage and Roy 1986). Moreover, the measurement of total plasma lipid fatty acids is more robust, analytically, because it circumvents the need for a pre separation into individual lipids (which inevitably incurs loss of analyte) prior to the preparation of the more volatile fatty acid methy esters which is a prerequisite for analysis by gas chromatography (Lepage and Roy 1986). Plasma lipids have been shown to be good indices of intake of EPA and DHA (Sanders, Lewis et al. 2006), are much easier to measure directly than phospholipids (Lepage and Roy 1986) and are widely used (Kuratko and Salem 2009).



### **5.1.5 Dietary analysis**

In order to ascertain the proportions of different fats and especially fatty acids, and to evaluate any change in relative proportions in the participants diet at baseline and then at one year, a dietary analysis method was required. A four day diary (Appendix 11.16) was used in this investigation and involved detailed food intake on two weekdays and two weekend days. This was because an individual's food and drinking habits may vary during the working week and over the weekend. This information would not be captured on a 24 hour recall dietary analysis. The four day food diary allowed detailed estimation of the energy and macronutrient intake as well as micronutrients for each participant and also allowed the participants' to describe portion size allowing an estimation of the quantity of food consumed to be made. With detailed descriptions of the foods consumed coding could be undertaken to give an accurate estimation of the energy, micro and macronutrient components of the diet. This accuracy guided selection of the four day food diary over a food frequency questionnaire which relies on accurate recall and does not detail portion sizes (Kipnis, Subar et al. 2003).

## **Data Collection methods**

### **5.1.6 Methods for Chapter 6: Reliability study**

#### **5.1.6.1 Measurements**

The range of motion measurements assessed in this study were: shoulder joint flexion, abduction, external rotation and hand behind back. Shoulder joint flexion and abduction were assessed using an inclinometer (Acuangle™, anglelevel) (Figure 5.1). The shoulder strength measurements assessed were; flexion, abduction, abduction in an internally and externally position of the shoulder, colloquially termed the empty and full can position respectively, shoulder internal and external rotation and elbow flexion and extension. The strength measurements were assessed using a JTech PowerTrack™ II Commander hand held dynamometer, using the concave pressure pad for comfort (JTech Medical, Salt Lake city, UT, USA) (Figure 5.2). The strength tests were all assessed with the participant sitting on a treatment plinth (with no back support) with their hips and knees at 90° and their feet flat on a footstool. The range of motion tests were assessed in standing.

#### **5.1.6.2 Raters**

The chief investigator and co-investigator were both musculoskeletal physiotherapists with more than 10 years of clinical experience. To ensure proficiency of use with the inclinometer and the hand held dynamometer both testers participated in a minimum of three hours training with both measurement tools.

#### 5.1.6.3 Assessment of participants

Participant's attended one assessment session of 150 minutes duration. All testing was carried out in a private room at Guy's Campus, King's College London. During testing the room temperature and lighting were kept constant and any external noise kept to a minimum to prevent distraction. At the assessment the participants were given a full verbal explanation of the testing procedure by the co-researcher (Hannah Dollings) and provided with an information sheet which clearly set out the purpose of the study (Appendix 11.7). Those willing to participate in the study were asked to sign and date the consent form (Appendix 11.8). Participants were required to expose their shoulders with male participants removing their shirts and female participants wearing vest tops. They were all asked to remove their shoes and socks.

Demographic data and subjective history information including height, weight, age, hand dominance, occupation and current sporting activities were recorded. Each participant was screened for any shoulder pathology using Neers test, Hawkin's and Kennedy, resisted shoulder external rotation and palpation of the greater tuberosity (Litaker, Pioro et al. 2000, Hegedus, Goode et al. 2008).

Each participant's shoulder range of motion was measured followed by their shoulder strength in each data collection phase. A computer generated randomisation sequence determined which shoulder was tested first for the participant and which examiner tested first. There was a fifteen minute break between each test each testing sequence taking approximately twenty five minutes in duration.

The break between testing sequences served to minimize examiner bias and the recollection of any previous measurements taken. The data collection sequencing was organised as follows: participant one measured by examiner A (first data collection phase for examiner A), simultaneously participant two measured by examiner B (first data collection phase for examiner B); fifteen minute break; participant one measured by examiner B (first data collection phase for examiner B), simultaneously participant two measured by examiner A (first data collection phase for examiner A); fifteen minute break: participant one measured by examiner A (second data collection phase for examiner A), simultaneously participant two measured by examiner B (second data collection phase for examiner B); fifteen minute break, participant one measured by examiner B (second data collection phase for examiner B), simultaneously participant two measured by examiner A (second data collection phase for examiner A). This process continued for all the participants.

#### 5.1.6.4 Shoulder range of motion assessment

Four physiological shoulder movements were measured in a consistent order, flexion, abduction, external rotation the functional movement of 'hand behind back', and were measured in two separate occasions on both shoulders of each participant by each of the two examiners. All the movements were measured in standing and followed a similar methodology (for flexion, abduction and external rotation) as described by Valentine and Lewis (2006). The participants

were asked to assume ‘a comfortable and natural standing position’. They were asked to gently flex and extend their head and to stop in a position which felt natural and comfortable and to flex and extend their shoulders and again stop in a position which felt natural and comfortable. Finally they were invited to take a breath and breathe out and adopt a standing posture which felt natural and comfortable.

The upper limb joint positions, placement of the instruments and tester position are detailed in Table 5.4. The tests were all conducted bilaterally. Each participant performed the movement three times and the examiner verbally relayed the measurements to an independent observer who recorded each set of measurements. The mean of the three values was used for data analysis, having been found more reliable than a single measure (Dollings, Sandford et al. 2011). The abduction and flexion measurements were recorded in degrees and the external rotation and hand behind back in centimetres and also anatomical landmarks for the hand behind back measurement.

Table 5.2 Upper limb joint positions, placement of measuring instruments and movements

<b>Movement</b>	<b>Inclinometer placement/ Tape measure placement</b>	<b>Movement</b>	<b>Position of investigator</b>
<b>Shoulder flexion</b>	Proximal end of inclinometer placed at deltoid insertion on anterior aspect of upper arm along shaft of humerus.	With elbow extended, participants were asked to raise their arm up in front of them leading with their thumb. In sagittal plan	Lateral to participant
<b>Shoulder abduction</b>	Proximal end of inclinometer placed at deltoid insertion on lateral aspect of upper arm along shaft of humerus.	Elbow extended, participants were asked to raise their arm out to the side and up, leading with their thumb. In 45° off sagittal and frontal planes	Lateral to participant.
<b>External rotation</b>	Measurement taken from radial styloid to umbilicus.	Elbow by the side of the body, flexed to 90° with the forearm in neutral. Participants were asked to ER until end of range. In frontal plane	In front of participant

<b>Hand behind back</b>	Measurement taken from C7 to radial border of the nail fold of the thumb.  Anatomical landmark also noted.	Shoulder internal rotation and elbow flexion, taking the hand as high as possible behind the participants back, leading with the thumb.	Behind participant
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Legend: C7= 7th cervical vertebrae, ER= external rotation

#### 5.1.6.5 Shoulder strength assessment

Participants were asked to assume a relaxed sitting posture and relax their upper limbs. The assessment protocol included testing seven different strength measurements; shoulder abduction, flexion, full can test and empty can test, external and internal rotation and elbow flexion. To ensure that the joint positions listed in the protocol were adhered to, the shoulder and elbow positions were measured using the inclinometer (Green, Buchbinder et al. 1998, Valentine and Lewis 2006). The upper limb joint positions, placement of the instruments and tester position are detailed in Table 5.3. The tests were all conducted bilaterally.

The concave testing pad for the JTech PowerTrack™ II Commander hand-held dynamometer (HHD) was selected for use in the investigation as it conformed to the contours of the forearm and was considered to be more comfortable for the participants. When pressure is placed on the testing pad the force is calculated and displayed in either pounds or Newton. The two PowerTrack™ II Commander HHDs used in the investigation were factory calibrated and automatically calibrated when they are switched on. The two HHDs were calibrated and checked for accuracy by the medical devices department at St Thomas' Hospital, London, UK for accuracy. Each participant was tested with the same HHD.

The tests were performed as 'make' tests (i.e. a maximal contraction exerted against a stationary dynamometer) and this was repeated three times with a five second rest between each contraction. A stopwatch was used to time the five second rest and also to ensure each isometric contraction lasted for five seconds. The testing was then repeated by the same investigator on the contra lateral shoulder. Following both shoulders being tested the participant had a break of 15 minutes. The testing procedure was then completed on both shoulders by the second investigator. All measurements were recorded in pounds. The order of investigators and shoulder testing were randomised by a computer generated randomisation chart.

Standardised instructions were read out to each participant during each isometric contraction: "Hold it there, don't let me move you (two seconds), now push as hard as you can, keep pushing, keep pushing and relax (three seconds)" (Sisto and Dyson-Hudson 2007). The investigators provided resistance with their dominant right hand. The muscle force generated during each test and displayed in pounds on the console was documented by an independent observer. The investigators and subjects were blinded to the measurements throughout. The observer also monitored the time taken between the tests.

Table 5.3 Detailing the position and resistance applied for each strength test

<b>Muscle test</b>	<b>Inclinometer placement</b>	<b>Testing position of limb</b>	<b>Body part stabilised</b>	<b>HDD placement</b>	<b>Investigator position</b>	<b>Direction of force</b>
<b>Shoulder abduction</b>	Proximal end of inclinometer placed at deltoid insertion on lateral aspect of upper arm along shaft of humerus.	Elbow extension, shoulder 10° abduction	Medial epicondyle	Lateral aspect of humerus, just proximal to the elbow	Lateral to subject, stride standing.	Medially directed force, perpendicular to limb.
<b>Shoulder flexion</b>	Proximal end of inclinometer placed at deltoid insertion on anterior aspect of upper arm along shaft of humerus.	Elbow extension, shoulder 10° flexion	Posterior elbow	Anterior aspect of humerus, just proximal to the elbow	Anterior to subject, stride standing.	Anterior to posterior force, perpendicular to limb.
<b>Full can test</b>	Proximal end of inclinometer placed at deltoid insertion on anterior aspect of upper arm along shaft of humerus.	Elbow extension, upper limb 90° elevation in scapular plane, forearm pronated with upper limb internally rotated.	Anterior elbow	Volar aspect of the forearm just proximal to volar wrist crease	Lateral and posterior to limb	Downward force, perpendicular to limb.
<b>Empty can test</b>	Proximal part of inclinometer placed at deltoid insertion on anterior aspect of upper arm along shaft of humerus.	Elbow extension, upper limb 90° elevation in scapular plane, forearm supinated with upper limb externally rotated.	Posterior elbow	Dorsal aspect of the forearm just proximal to dorsal wrist crease	Lateral and posterior to limb	Downward force, perpendicular to limb.

<b>Muscle test</b>	<b>Inclinometer placement</b>	<b>Testing position of limb</b>	<b>Body part stabilised</b>	<b>HDD placement</b>	<b>Investigator position</b>	<b>Direction of force</b>
<b>Shoulder external rotation</b>	Distal part of inclinometer placed at lateral wrist crease along radius	Upper arm in a neutral position at trunk, elbow flexed to 90°, forearm in a neutral position so palm facing inwards	Medial wrist	Dorsal aspect of forearm with distal part of pad at dorsal wrist crease	Lateral to subject stride standing	Medially directed force, perpendicular to limb.
<b>Shoulder internal rotation</b>	Distal part of inclinometer placed at lateral wrist crease along radius	Upper arm in a neutral position at trunk, elbow flexed to 90°, forearm in a neutral position so palm facing inwards	Medial wrist	Volar aspect of forearm with distal part of pad at volar wrist crease	Medial to limb, lateral to subject, stride standing	Laterally directed force, perpendicular to limb.
<b>Elbow flexion</b>	Distal part of inclinometer placed at lateral wrist crease along radius	Upper arm in a neutral position at trunk, elbow flexed to 90°, forearm supinated	Posterior wrist	Volar aspect of forearm with distal part of pad at volar wrist crease	Lateral to subject	Downward force, perpendicular to limb.

Figure 5.1 Inclinometer



Figure 5.2 The JTech Power Track II Commander HHD



Figure 5.3 Positioning of participant on plinth in a relaxed seated posture for the strength assessment.



#### **5.1.7 Methods for Chapter 7; Shoulder pain and the use of nutritional supplements: A questionnaire based investigation**

A descriptive cross sectional survey methodology was employed using paper based questionnaire booklets (Appendix 11.12). Questionnaires are the most commonly used tool in survey research (Shaughnessy, Zechmeister et al. 2011) and it was felt that this was the best method available to collect the required data. A paper based questionnaire was selected to ensure ease of completion at the eight different research sites where on-line surveys might have been more difficult and introduced a bias in that only those proficient with computer use might have taken part. It also importantly allowed participants to feel under no obligation to participate as it was their decision to return the questionnaire or not. This process also allowed the participants to complete the questionnaire at a location of their choice and taking as much time as they required.



#### **5.1.7.1 Data collection**

The data collection period spanned six months from September 2011 until February 2012. Potential participants with a diagnosis of shoulder pain were invited to participate in the study by their treating physiotherapist. Those who expressed an interest in taking part were given a participant information sheet to read and were encouraged to discuss with their physiotherapist as well as family or friends (Appendix 11.10) to help inform the decision whether to participate or not. Participants were aware that their decision to participate or not would not influence the treatment that they would receive. On the next visit to the clinic (on average one week later) those who were still interested in taking part completed a witnessed informed consent document (Appendix 11.11). They were then given the set of questionnaires in a booklet form (Appendix 11.12). The questionnaire booklet took approximately 30 minutes to complete and the participants were informed they could complete the forms before or after their clinic visit or if they preferred, at home. Once the questionnaire was completed it was placed in an envelope that was provided with the booklet and securely sealed. There was no identifiable personal information contained in the questionnaires or the envelopes. Subjects were required to complete these forms on one occasion only. The participant then returned the envelope to their treating physiotherapist and this marked the end of their involvement in the study.

Each questionnaire was coded for the site where the participant was recruited. Once the set of questionnaires had been completed at each site or the end of data collection period (end February 2011), whichever was sooner, the completed anonymised questionnaires were returned by secure special delivery (Royal Mail) to JL (co-supervisor) at an NHS site. The booklets were then securely stored in a locked cabinet in a locked office.

#### **5.1.8 Methods for chapter 8; the efficacy of long-chain omega-3 PUFAs and exercise in the treatment of rotator cuff tendinopathy: a randomised controlled trial.**

##### **5.1.8.1 Study design**

A two arm parallel randomised placebo-controlled trial was chosen as the design for this study as the longevity of the study and the prolonged washout period required would make a cross over design impractical. Participants were randomly allocated to treatment.

The treatment allocation (Group A or Group B) was effected by Professor Tom Sanders, Kings College London (primary supervisor) who was not involved in the data collection component of the study. The allocation of treatment (A or B) was held by Professor Sanders and was concealed

until the study was completed and data for the primary and secondary outcomes had been entered into the statistical database.

#### 5.1.8.2 Controlling bias

Bias in research investigations is defined as an inclination towards prejudiced consideration of a research question and undermines the finding and conclusions of a research investigation (Pannucci and Wilkins 2010). Bias is not a dichotomous entity, it is present to some extent in every investigation (Pannucci and Wilkins 2010) and can occur at any point in the research process.

There are two types of bias;

- Random bias where results are due to sampling variability or measurement error. This is most commonly detected and corrected with statistical analysis (Sica 2006)
- Systemic bias where reproducible errors and inaccuracies produce false values and distort the investigation. This is very difficult to determine as it is down largely to human nature (Adebiyi 2010).

Sources of bias include, flawed study design, selection bias, measurement bias, intervention bias and reporting bias (Sica 2006). In order to mitigate against these potential sources of bias, the following was methods were utilized.

- Randomisation: refers to the process of assigning participants to trial treatment groups. This helps ensure that the treatment groups will be comparable for both known and unknown variables (Beam 2002). Within this study a computer generated unpredictable randomisation code was created prior to the study starting and was not broken until all data analysis was complete. It was kept sealed and locked in a cabinet within Professor Sander's office at Kings College London.
- Allocation concealment: refers to the technique used to ensure that the randomisation sequence is applied without the person assigning the participants to the treatment groups knowing what the next treatment would be (Dettori 2010). In this study the person assigning the participant study code and therefore treatment group had no knowledge of which supplements (the placebo or long-chain omega-3 PUFA) were in the sealed opaque containers which bore the participant number on them and numbers were given sequentially to participants. It would have been impossible for the person assigning to the

treatment groups to know which supplement corresponded with which participant number.

- Placebo control: refers to the use of a sham treatment that is designed to have no real effect as a comparator to the active treatment (Wang 2003). In this study a placebo supplement which simulated the long-chain omega-3 PUFA in every way other than the ingredient long-chain omega-3 PUFAs was used.
- Blinding: refers to the process of concealing the assigned treatment from those participants in the study (participant blinding), from those involved in their treatment (treater or care giver blinding) and from those collecting, managing and analysing the data (assessor blinding) so that the knowledge of treatment group does not influence their practice or behaviour (Day and Altman 2000). Adequate blinding of all three categories (participant, treater and assessor blinding) results in a double-blind trial. Blinding as carried out in the following ways within this trial:
  - Participant blinding; participants were blinded to the treatment group they were allocated. The placebo and long-chain omega-3 PUFA supplements looked the same in appearance and both were flavoured with peppermint to try and prevent any fish odour from the long-chain omega-3 PUFA supplements.
  - Treater or care-giver blinding; the physiotherapists in the shoulder exercise class were aware that the participant was on the trial but were not aware of their study number nor which supplement they were taking.
  - Assessor blinding; the assessors were unaware which participant numbers corresponded to which supplement until data analysis had been completed.
  - Intention to treat analysis includes all the participants of a trial in the treatment group to which they were assigned at the start of the trial. It is regardless of their adherence to the treatment, whether they received the assigned treatment or not and regardless of whether they withdrew from the study. (Gupta 2011). The concept is summed up by “once randomised, always analysed” (Wertz 1995). The data within this study was analysed on an intention to treat basis.

#### 5.1.8.3 Outcome points

Outcomes were measured at baseline, after the intervention (two months), at three months, six months and one year. The study took place between 18/12/2008 and 18/1/2013. The primary outcome point was at two months, which corresponded with the end of treatment intervention and aimed to detect the combined change in outcome measures corresponding with the completion of the shoulder exercise class and the supplements. The three and six month assessment points were included to assess any changes following cessation of the intervention. The one year assessment marked the end of each participant's involvement in the study and represented the longevity outcome. Follow up at one year was deemed necessary to provide adequate follow up time for assess outcomes in patients with RC tendinopathy. This time point has been used in other investigations (Haahr, Ostergaard et al. 2005, Kukkonen, Joukainen et al. 2014, Littlewood, Bateman et al. 2016).

Table 5.4 data collected at each time point

Data Collected	Baseline	2 months	3 months	6 months	12 months
Demographic information	•#				
Symptomatic shoulder	•#				
Dominance	•#				
Weight (kg)	•#				•
Height (cm)	•#				•
Duration of symptoms	•#				
Onset: Trauma / non-traumatic	•#				
Nature of symptoms: Constant pain / Pain only with movement	•#				
Night pain: Yes / No	•#				
Possible to sleep on painful side: Yes / No	•#				
Analgesic use	•#				
Smoking: No / Yes (if yes, how many?)	•#				
Neer's impingement sign	•#				
Hawkins impingement test	•#				
Palpation of greater tuberosity	•#				
Bilateral shoulder ROM with NRS: Flexion, Abduction, ER, Hand behind back	•	•	•	*•	*•

Bilateral shoulder strength: Abduction, ER & IR, Elbow flexion, 'Full can' test, 'Empty can' test	•	•	•	•	•
Disability scores (OSS and SPADI)	•	•	•	•	•
NRS	•	•	•	•	•
Patient specific functional score	•				
Quality of life measures (SF 36 and EQ5D3L)	•	•	•	•	
Global Impression of Change		•	•	•	•
Blood tests	•	•			
4 day food diary	•				•

Legend: NRS (Numerical Rating Scale), ROM (range of motion), ER (external rotation), IR (internal rotation), OSS (Oxford shoulder score), SPADI (shoulder pain and disability index), SF 36 (short form 36), EQ5D3L (EuroQol 5D3L) • (information collected at specified timepoint) #=pre randomisation

#### **5.1.8.4 Interventions**

##### **5.1.8.4.1 Supplements**

The active treatment used in this trial MaxEPA (Seven Seas Ltd, Hull, UK, MHRA product licence 19488/0353). These capsules were provided as opaque gelatine coated capsules, oval in shape and brown tan in colour to disguise the content, containing 170mg EPA, 115mg DHA, 2 units/g tocopherols acetate (vitamin E). The placebo supplement looked identical and contained a mixed inert oil (olive oil BP containing the same amount of vitamin E and antioxidants as the active treatment) and did not contain any EPA or DHA with the EPA and DHA being replaced by oleic acid. Participants in both groups were asked to take nine soft shell capsules per day for a total of two months. The capsules were supplied in identical plain white plastics tubs which had a tamper proof seal. Each participant was supplied with three tubs of capsules containing 201 capsules per tub, 603 in total. The participants were requested to return any unused capsules at the end of the study.

The participants were provided with verbal and written instructions on how to take the capsules. It was suggested that they took the capsules three times a day with breakfast, lunch and dinner to aid adherence to the supplement regime. Patients were advised however, that they could take them in any number, up to nine at one time, and at any time of the day but advised to always take them with a drink, during or just after a meal, in order to aid their digestion and minimise any possible side effects.

A label on the outside of the container reminded the participants that nine capsules should be taken per day. The label also provided contact details for the chief investigator should any participant have any concerns or questions. They were instructed not to store the capsules in direct sunlight or above 25°C to prevent any oxidation of the oils.

The decision to use MaxEPA supplements was based on the availability of a matched placebo supplement. MaxEPA is also available to prescribe and is featured in the British National Formulary 55<sup>th</sup> edition, 2008 (Joint, Formulary et al. 2008).

The dose level of 2.6g/d was based on similar studies showing beneficial effects on inflammatory musculoskeletal disorders at similar doses (discussed in Chapter 4).

#### **5.1.8.5 Duration**

Eight weeks was selected as the supplement intervention duration period in this study. This time frame was chosen as it has been reported that it takes eight to twelve weeks until the benefits of taking the supplements are noticed in clinical outcomes (Fortin, Lew et al. 1995, James and Cleland 1997).

Studies also suggest that an intake of four weeks might be sufficient to effect an anti-inflammatory change (Healy, Wallace et al. 2000, Yaqoob, Pala et al. 2000). Maximal increases in EPA into the phospholipids were observed in both studies four weeks after starting supplementation. Further evidence to support this decision is presented in Chapter 4.

The participants in this study attended a structured shoulder class for eight weeks. In order to aid adherence and avoid unnecessary follow ups it was decided that this too should be the duration of supplementation, given that the optimal duration of supplementation is currently unknown.

#### **5.1.8.6 Quality assurance**

A sample of the remaining capsules was returned to Seven Seas after the study had finished for analysis to confirm that they were MaxEPA and placebo capsules and to ensure that no oxidation of the oils had taken place. The laboratory results confirmed that the capsules were as stated and that the levels of EPA and DHA in the MaxEPA capsules were as expected. The results also confirmed that no oxidation of the oils had taken place (Appendix 11.17).

#### **5.1.8.7 Dietary Intake**

A four day food diary was used to assess dietary intake at baseline and 12 months (Appendix 11.16). These were then coded and analysed using NetWISP version 3.0 (Tinuviel Software, UK) by the CI.

#### **5.1.8.8 Rotator Cuff tendinopathy exercise group**

Participants were asked to attend the RC exercise group once a week for a period of eight weeks (eight classes in total). The RC exercise group involved education and advice and a ten station circuit. Each class was approximately one hour in duration.



#### **5.1.8.8.1 Quality assurance and standardisation of exercise group between sites**

In order to standardise this intervention the same exercise group was run in each of the four participating sites. Standardised exercise pictures and booklets to follow were produced (Appendix 11.19) and it was ensured that the exercise classes were run with a choice of timings to enable ease of attendance and maximise recruitment.

#### **5.1.8.8.2 Format of rotator cuff exercise group**

The study exercise programme consisted of a ten minute warm up, ten exercises of thirty seconds duration, each designed with three levels of progression to accommodate each participant's ability, a ten minute warm down and a ten minute education/advice session. The exercises aimed to improve strength of the RC muscles, improve proprioception, and encourage the transference of strength from the lower limb to the upper limb. They also aimed to improve exercise tolerance. The topics covered during the eight education sessions included; shoulder anatomy, pain, pacing and coping with flare ups, benefits of exercise and mobilisations, role of diagnosis and imaging, relaxation techniques and questions and answer sessions. Classes were run with a maximum of 15 participants and were run with two physiotherapists attending and one physiotherapy assistant. One of the exercise stations included manual therapy where a physiotherapist would perform manual therapy techniques on the study participants. Their techniques typically involved Mulligan Mobilisation with Movements (Kachingwe, Phillips et al. 2008, Teys, Bisset et al. 2008, Teys, Bisset et al. 2013) and were included to facilitate improvements in shoulder range of motion and function, as well as to help reduce pain.

This format of incorporating exercise with education and advice conducted under the guidance of a physiotherapist is the recommended best practice treatment approach for RC tendinopathy (BMJ 2013).

Participants were also requested to continue their exercise program at home. To facilitate this, an exercise booklet was provided (Appendix 11.19). Participants documented in their study diaries (Appendix 11.20) how many exercise sessions they managed to complete each week and any comments relating to their symptoms, the exercises or the supplements.

#### 5.1.8.9 Recruitment of participants

The study aimed to recruit men and women aged 18 to 80 years, who were referred for physiotherapy at one of four physiotherapy departments within the UK NHS.

The four participating physiotherapy departments were:

- St Thomas' Nation NHS Trust Hospital, Waterloo, London SE1
- Guy's Hospital, London Bridge, London SE1
- St George's NHS Trust, Tooting, London SW18
- Health at the Stowe, Westminster Primary Care Trust / Central London Community Healthcare NHS Trust, W2

All patients referred from general practitioners, extended scope practitioners and medical and surgical consultants with a diagnosis of RC tendinopathy at the four participating physiotherapy sites were considered for appropriateness to participate. Patients were deemed suitable for inclusion in the study if they met all of the inclusion criteria and did not fulfil any of the exclusion criteria (Table 5.5) Patients fulfilling the inclusion criteria and interested in taking part in the research study were asked by their physiotherapist to read the patient information leaflet (Appendix 11.14) and informed that the chief investigator or secondary investigator would be in telephone contact in the following week to discuss the study in greater depth and answer any questions. During the subsequent telephone conversation the screening questions were reassessed, and the study protocol described to the potential participant. If the potential participant provided verbal consent to take part in the research an appointment was arranged within the Guy's and St Thomas' Trust Clinical Research facility located at St Thomas' Hospital, London SE1, to perform screening tests, obtain written consent and to conduct the baseline assessment.

Table 5.5 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Unilateral shoulder pain of more than 3 months duration (anterior &/or antero-lateral location)	1. Known allergy to fish or fish products.
2. Pain produced or increased during flexion &/or abduction &/or external rotation of	2. Unwilling to take fish oils
	3. Currently taking high dose fish oils (over 1g daily).

the symptomatic shoulder.	4. Diabetes
4. At least four of the following:	5. Pregnancy or breast feeding
-positive Neer's impingement sign	6. Reproduction of shoulder symptoms during active cervical spine movements
-positive Hawkins & Kennedy test	7. Post traumatic onset of symptoms
-pain & weakness reproduced on full &/or empty can test.	8. Radiographic or clinical evidence of shoulder instability (sulcus, anterior/posterior draw, relocation test, apprehension test).
-pain & weakness on resisted shoulder external rotation	
-pain on palpation over greater tuberosity of humerus.	
5. Absence of exclusion criteria	

#### 5.1.8.9.1 Justification for inclusion criteria

The accurate diagnosis of RC tendinopathy is recognised to be problematic (Lewis, McCreesh et al. 2015) with special orthopaedic tests having questionable validity and role (Hegedus, Goode et al. 2012, Lewis, McCreesh et al. 2015) (see Chapter 3.3.2). However, clinically combinations of special orthopaedic tests are used to aid diagnosis, (Somerville, Willits et al. 2014, van Zuydam, van Rensburg et al. 2015). These include; Neer's impingement sign, Hawkins Impingement test, and palpation of the greater tuberosity. Other similar investigations have used these the same diagnostic criteria for RC tendinopathy as those used within this study (Ludewig and Borstad 2003, Littlewood and May 2007, Lombardi, Magri et al. 2008).

#### 5.1.8.9.2 Justification for exclusion criteria

Known allergy to fish or fish products/unwilling to take fish oils; this is due to the fact that the active supplements were derived from fish with no vegetarian option available.

Currently taking high dose fish oils (over 1g daily); this would have meant that the subject may have already been taking a 'therapeutic dose', thereby possibly negating any potential benefit from taking a high dose.

Pregnancy or breast feeding; due to possible complications of the high dose long-chain omega-3 PUFA crossing the placenta or transferring into the breast milk and ethical restrictions.

Reproduction of shoulder symptoms during active cervical spine movements: as this would have been indicative of symptoms originating from the cervical spine rather than the RC. Pain from the 5<sup>th</sup> or 6<sup>th</sup> cervical vertebrae often refers to the shoulder (Carette and Fehlings 2005).

Post traumatic onset of symptoms: this may represent a different patho-aetiology than non-traumatic tendinopathy (Sørensen, Bak et al. 2007).

Radiographic or clinical evidence of shoulder instability (sulcus, anterior/posterior draw, relocation test, apprehension test): this would suggest that the symptoms are originating from the shoulder instability rather than RC tendinopathy (Magee 1997).

Conditions such as diabetes and rheumatoid arthritis were excluded because of the known adverse effects of the conditions on healing and tendon status and their potential to introduce confounding influence on the study findings (Chen, Shapiro et al. 2003, Miranda, Viikari-Juntura et al. 2005, Pegreffi, Paladini et al. 2011, Titchener, White et al. 2014, Zakaria, Davis et al. 2014, Lin, Lin et al. 2015).

Although RC tendinopathy most commonly affects people over the age of 40 years it can affect people of all ages (Carr and Harvie 2005) and so men and women from 18 to 80 years were recruited into the study.

### **5.1.9 Participant flow through the investigation**

#### **5.1.9.1 Consent and randomisation**

On attending the first appointment at the clinical research facility the participant's involvement in the study was further discussed and any questions answered before written consent (Appendix 11.15) was obtained. Participants were consented into the study by the CI or the co researcher (Hannah Dollings). Both researchers had completed good clinical practice training and had been qualified as physiotherapists for over 10 years. Once consent had been given the participants were assigned a sequential study number. This study number corresponded to a container of supplements which had either been filled with supplement A

or supplement B. The randomisation of the supplements was computer generated by Professor Tom Sanders who kept the code sealed until after all data had been collected and entered into data spreadsheets for analysis. This occurred in August 2014.

### 5.1.10 Outcome measures

The primary outcome measure was the Oxford Shoulder Score (assessing self-reported disability). This has been previously described at the beginning of this chapter.

The secondary outcome measures are presented in table 5.6.

Table 5.6 Secondary outcome measures

Outcome measures
<ul style="list-style-type: none"> <li>• Numerical rating score for pain</li> <li>• Shoulder pain and disability index (SPADI)</li> <li>• Patient specific functional score (PSFS): a questionnaire used to quantify activity limitation and measure functional outcome in areas chosen by the patient specifically</li> <li>• EuroQol D5-3L (EQ-D5-3L) health questionnaire: a measure of health related quality of life</li> <li>• Short Form-36</li> <li>• Global rating of change</li> <li>• Range of glenohumeral range of motion (flexion/abduction/internal and external rotation, hand behind back)</li> <li>• Shoulder strength (shoulder flexion/abduction/full can and empty can/internal and external rotation and biceps strength)</li> </ul>

#### 5.1.10.1 Secondary outcome measures selected

The self-reported disability measure (SPADI), pain measure (NRS), restoration of function measure (PSFS), health related quality of life measures (EQ5D-3L and SF36) and global rating of change (GROC) have all been described previously in this chapter.

In studies investigating RC tendinopathy a reduction in range of motion and strength has been consistently reported (Lewis, McCreesh et al. 2015). The assessment method for measuring ROM and strength by both the CI and co-researcher demonstrated excellent clinical reliability as shown in the reliability study presented in Chapter 6.

Impairment measures are commonly used in clinical practice and therefore they were included in the battery of assessments for this study. However it is noted that they generally have a low responsiveness (Croft, Pope et al. 1994, Terwee, de Winter et al. 2005) which limits their ability to detect clinically important change in a patient's health over time.

#### **5.1.10.2 Calibration of measuring devices**

The accuracy of the tape measure was checked monthly, comparing 1cm on the tape to 1cm on a metal ruler. To ensure accuracy of the inclinometer the CI calibrated the inclinometer scale (displayed in 2° increments) against an electrical inclinometer (Saunders Digital Inclinometer; the Saunders Group, Chaska, Minnesota, USA). The JTech Power Track II Commander was calibrated according to the manufacturer's instructions by the biomedical physics department at St Thomas' NHS Trust on an annual basis.

#### **5.1.10.3 Format and standardisation of assessments**

The baseline evaluation included history taking, impairment measures, and completion of outcome questionnaires, weight, height and measurement of waist circumference. Blood samples were taken by one of the two clinical research facility nurses (registered nurses).

A 5ml sample was taken and collected in an EDTA and plasma tube, processed and frozen at -80°C for analysis at the end of the study. In order to ensure standardisation of this assessment between participants and over time, a specific assessment order was adhered to:

1. Study, including involvement required by the participant was verbally reviewed and any questions answered.
2. Screening tests for RC tendinopathy performed; (Neer impingement sign (Neer 1983), Hawkins-Kennedy impingement test (Hawkins and Kennedy 1980), palpation of greater tuberosity (Xiao, Cui et al. 2010) and pain on resisted shoulder abduction and /or external rotation) (O'Kane and Toresdahl 2014). Absence of exclusion criteria checked.

3. Written consent obtained
4. Study participant number issued
5. Venous blood sample taken from the median cubital or cephalic veins at the elbow by the clinical research facility nurse.
6. Weight, height and waist circumference measured as detailed above in section 5.2.3.
7. Subjective history taken (Appendix 11.18)
8. Impairment measures in the following order; ROM for shoulder flexion, abduction, external rotation, hand behind back, strength testing (make tests) for shoulder flexion, abduction, empty can and full can test positions, internal and external rotation and elbow flexion. The positions and method used are those described in the reliability range of motion study undertaken by the CI and co researcher and presented in Table 5.2.
9. Participant completed outcome measures in the following order; OSS, SPADI, PSFS, EQD5, SF36.
10. Questionnaires checked by investigator for completeness.
11. Instruction on completion of the diary sheet and the four day food diary.
12. Three containers of capsules and instructions on how to take them, issued.
13. Follow up appointments arranged and a CI contact details card given.

The participants were advised as to the possible side effects of the supplements, that included; stomach upset and dark stools, and were advised to contact the CI or co-researcher if they experienced any adverse effects or concerns. Participants were asked to document in their exercise diary how many capsules they had taken each day, if there were any side effects, how much exercise they had carried out or if they had attended the exercise group and to note any other comments they wished to share.

### ***Two month assessment- Immediately post treatment***

The CI (or co-researcher in the absence of CI) reassessed the participants following the completion of the supplements and exercise class. This assessment took place approximately eight weeks from baseline. The assessment involved the same questionnaires and physical tests as baseline and blood tests. In addition, the participants were asked to rate any

improvement or regression as a percentage improvement or worsening from baseline. The participants were asked to hand in their completed exercise and supplement diary sheets, their completed four day food diary if they had not already returned it by post and any unused capsules. Participants were asked to continue their exercises as instructed following the exercise class.

### ***Three and six month assessments***

Participants were assessed at three and six months by the CI (or co-researcher) using the same questionnaires and physical tests as in assessment at two months. All outcome measures assessed at baseline were completed. No blood tests were taken at these assessments. In addition, participants were also asked if they were still doing their exercises and also the frequency, nature and duration of exercises.

### ***Twelve month assessment***

One year assessment occurred at approximately one year from baseline. This assessment replicated the three and six month assessments. In addition, the participants were sent a 4 day food diary a week prior to their appointment for assessment which they were asked to return at the time of their final assessment. At the end of the one year follow up assessment the participant's involvement in the study was finished.

#### **5.1.10.4 Observation of the assessment of the participants**

Matt Morrissey PhD (supervisor prior to leaving Kings College London, London, UK) and Jeremy Lewis PhD (co-supervisor) observed the CI and the co-researcher during an initial participant assessment. This was to ensure quality and consistency of the assessment procedures and that the methods used to obtain consent were considerate and appropriate.

#### **5.1.10.5 Ascertaining adherence to the intervention**

Plasma fatty acid analysis, capsules returned and self-report numbers of capsules taken were all used as measures of adherence with the supplement intervention. Attendance at the exercise class and documentation of exercises undertaken gave an indication regarding the adherence with the exercise intervention. Excellent attendance was rated as eight classes attended out of eight, good attendance as six or seven classes, satisfactory attendance as four or five classes and poor attendance as three or fewer classes attended.



#### **5.1.10.5.1 Markers of compliance to the supplement intervention**

Blood plasma levels of EPA and DHA were measured using gas chromatography. The relative proportions of fatty acids within the plasma total lipids were evaluated using a one-step direct transesterification procedure (described below). Following supplementation with DHA and EPA a corresponding rise in levels of the DHA and EPA in the plasma total lipids were expected (Sanders, Lewis et al. 2006). This has been used as a measure of compliance to long-chain omega-3 PUFA intervention in other studies (Sanders, Hall et al. 2011, Hall, Hay et al. 2013).

Any unused capsules were returned and counted to give a returned pill count. This was then subtracted from the number of capsules given (603) and the number of capsules consumed by the participant calculated. Pill count is another commonly used measure of compliance and has been recommended as the standard for assessing medication adherence in clinical trials and practice (Lee, Grace et al. 2007). The tally of the number of capsules taken recorded daily in the study diary (Appendix 11.20) was also noted.

#### **5.1.10.5.1.1 Venepuncture**

Blood samples at baseline and two months at the end of intervention were obtained following fasting (nothing but water) from 10pm the previous evening. All blood samples were undertaken by a trained phlebotomist working within the clinical research facility. As per facility protocol, thorough hand washing procedures were performed prior to each blood sample being taken. A tourniquet was applied around the upper arm and tightened. An antiseptic swab was then used to clean the ante brachial fossa where the blood was to be taken from. The vacutainer method (Becton-Dickinson, Oxford, UK OX4 4DQ) was used. The needle was screwed into the disposable vacutainer holder, unsheathing it, and inserting it into the median cubital or cephalic vein with minimal pressure. The vacutainer was then attached and the tourniquet released. The samples were collected in EDTA anticoagulated tubes.

#### **5.1.10.5.1.2 Sample processing**

After collection the vacutainers containing the blood were inverted ten times. They were kept at room temperature and allowed to stand for a minimum of 30 minutes, but not more than one hour, to allow for clotting before centrifugation. They underwent centrifugation for 15

minutes at 1300 revolutions per minute (RPM) at 4°C. The plasma and serum were then pipetted into two x 1ml aliquots for storage.

### 5.1.10.5.1.3 Coding and storage of samples

The vacutainers were all labelled prior to each visit with the subject ID, initials and date of birth using a permanent marker. Eppendorf tubes (2.0ml everyday SC Microtube Skirt NS) were labelled prior to each visit using permanent marker. The format of the labelling is depicted in Figure 5.4.

Figure 5.4 Labelling used on Eppendorf tubes

CI	Study name	ID number and initials	visit
FS	Sh	01/ XX	1
Test: Serum/plasma			
Date: 10.10.2010			

Legend: CI (chief investigator), ID (Identification), FS (Fiona Sandford), SH (shoulder) visit 1 states visit they were attending –pre or post intervention blood sample.

Cryovial boxes were used to store the samples in the -80°C freezers at Kings College London Franklin Wilkins building, Waterloo campus or the clinical research facility. Several participants' samples were stored in one box. Each box was clearly labelled with the CI's name, Kings College London, the study name, the ethics reference, the type of samples, the date of the initial and end sample collection and the contact number of the CI. The samples were placed in the -80°C freezers no more than 10 hours following collection and kept in a 4° refrigerator until point of freezing. Ten hours at 4° is considered an acceptable time frame as whole blood stored at room temperature for seven days showed only very minimal changes in a wide range of analytes, including lipids (Clark, Youngman et al. 2003). Similarly analyte stability has been found to be preserved for up to five years when stored at -80°C (Clark, Youngman et al. 2003). The storage of samples at -70°C was found to be preferable than at -20°C with regards to analyte stability (Cray, Rodriguez et al. 2009).

#### 5.1.10.5.1.4 Analytical methods

A one-step direct transesterification procedure was used to determine the fatty acid composition of the plasma samples collected. This method was adapted from the one described by Lepage and Roy (1986) and is the method used commonly for this type of analysis within the Nutritional Sciences Laboratory at Kings College London, London UK (Lepage and Roy 1986). The principal behind the method is that total lipids are transesterified with hydrogen chloride as a catalyst in a methanol:toluene solution. Gas chromatography, in the presence of a 15:0 internal standard, is then used to perform the fatty acid methyl ester analysis. The reagent is produced by adding acetyl chloride to methanol. An internal standard is 50mg pentadecanoic acid/ml, methanol:toluene (4:1 by volume).

Table 5.7 Materials used, and their suppliers, for fatty acid extraction.

Item	Supplier
Toluene AR	BDH Merck Ltd, Poole, Dorset UK
Hexane Puriss	BDH Merck Ltd, Poole, Dorset UK
Methanol AR	BDH Merck Ltd, Poole, Dorset UK
Acetyl chloride AR	BDH Merck Ltd, Poole, Dorset UK
6% potassium carbonate in distilled water	BDH Merck Ltd, Poole, Dorset UK
Internal standard: pentadecanoic acid	Sigma, BDH Merck Ltd, Poole, Dorset UK
External standards: Sigma 189-1, 189-2, 189.3	Sigma, BDH Merck Ltd, Poole, Dorset UK
MaxEPA	Seven Seas Ltd, Hull, UK
BPX70 column (25 m X 220 µm X 0.25 µm)	SGE Analytic Science, Milton Keynes
Gas chromatography	Agilent 7890A GC; Agilent Technologies

Legend: AR= authentic reference, µm=micrometre, GC=gas chromatography. MaxEPA (PUFA supplement, seven seas). Internal standard = 50mg pentadecanoic acid/ml, methanol:toluene (4:1 by volume).

The internal standard was prepared by adding 5ml of 1mg/ml internal standard in methanol to 75ml methanol. Toluene was then added to this solution to make up to a total of 100ml. The solution was chilled on ice in a conical flask and acetyl chloride (10ml) was added drop-wise whilst swirling the flask in a fume cupboard. The reagent was cooled before using. It remained stable for two weeks at room temperature.

Fatty acid methyl ester standards of Sigma 189-1, 189-2 and 189-3 dissolved in hexane 1mg/ml and fatty acid methyl ester of MaxEPA as a reference standard for DHA and EPA dissolved in hexane 1mg/1ml.

#### **Sample preparation:**

Samples were prepared by pipetting 0.1ml plasma into a tube fitted with a Teflon lined screw cap (16x25mm) using a positive displacement pipette. Then 2.2ml of internal standard solution was added to the tube. The tube was then sealed and heated in a water bath for two hours at 60°C. Once cooled, 5ml of 6% potassium carbonate was added and the sample was centrifuged at 2500rpm for 10 minutes. The upper phase was then transferred into an amber vial for gas chromatography analysis.

Fatty acid methyl esters (FAMES) were separated on an Agilent 7890 Gas Chromatograph (GC) (Agilent Technologies, Santa Clara, CA, USA) fitted with a flame ionization detector with a 25m BPX70 column (SGE Analytical Science, Milton Keynes, UK). In order to establish the identities of the GC separated FAMES and hence the parent fatty acids, the chromatographic peak retention times of the sample chromatograms were compared with those obtained from the analysis of authentic reference standards (FAME mixtures: 189-1, 189-2, 189-3 spanning the long-chain class: 14:0-22:6n-3) run under identical GC conditions. Giving the elution order of the FAMES as supplied by the manufacturer, the chromatographic peaks were labelled through peak retention time matching. For quantitative analysis, the time integrated flame ionization detector (FID) responses (peak areas) for the sample chromatograms were tabulated for each FAME species. The proportion in percentage terms by weight of each fatty acid was calculated by expressing the peak area of each species as a percentage of the total area by summation (excluding the 15:0 internal standard reference peak).

#### **5.1.10.5.1.5 Calculations:**

The fatty acid composition was calculated as per the equation below:

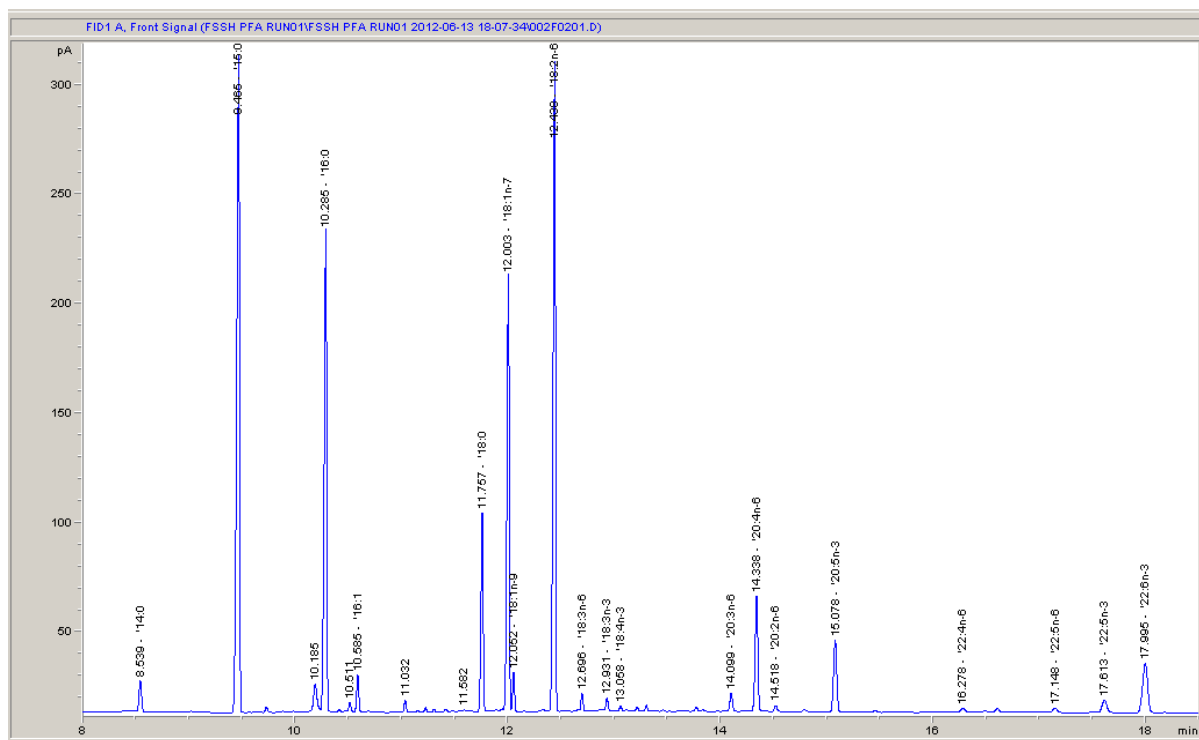
$$\text{Fatty acid composition} = \frac{\text{area of fatty acid interest}}{(\text{total area} - \text{area of internal standard})}$$

Table 5.8 Operating conditions of gas chromatography (Agilent 7890A)

<b>Injector</b>	
Type	Front injector
Injection volume	5ml
<b>Inlet detector</b>	
Injection mode	Split 50:1
Inlet temperature	240°C
<b>Gas</b>	
Carrier gas	Hydrogen at 1 ml/minute
Make up gas	Nitrogen
<b>Column</b>	
Column	BPX 70 SGE (25 m x 220 m x 0.25m).
<b>Oven</b>	
Temperature/programme	Initial temperature 160°C, held for 4 min, then ramped 10°C/min for 10 min to 200°C, then 40°C/min for 10 min to 240°C.
Run time	29 min
<b>Detector</b>	
Type	Front Ionisation Detector (FID)
Detector temperature	250°C
Data acquisition rate:	20Hz

An example of the GC trace can be seen below showing the peaks of the different fatty acids identified by retention time with standards of known composition obtained from Sigma Aldrich (BDH, Poole, Dorset).

Figure 5.5 Gas chromatogram trace of fatty acid methyl esters from a plasma sample including the internal standard 15:00 methyl ester.



#### 5.1.10.6 Adverse events

Adverse events were defined as side effects due to taking the supplements or the exercise therapy which required medical intervention.

### **5.1.11 Methods for Chapter 9: Exploring barriers, motivators and enablers to nutritional supplement use and exercise in rotator cuff tendinopathy: a qualitative study.**

#### **5.1.11.1 Study design**

Qualitative methods were employed to explore factors affecting adherence to a prescribed exercise programme and with taking the provided supplements. They were considered the most appropriate method to use to yield the breadth of information required (Patton 2002). Qualitative research is exploratory by nature, used to further understand and discover people's beliefs, attitudes and behaviour (Barker, Pistrang et al. 2002). It is used to understand the reasons behind decisions and behaviours. It uses unstructured information gathered through a variety of methods such as focus groups, interviews and survey or correspondence (Patton 2002). Smaller sample sizes are generally required in qualitative research than quantitative research due to the breadth of information acquired from each participant (Marshall and Rossman 2006).

#### **5.1.11.2 Data collection**

Interviews were conducted by the physiotherapist researcher (CI) in a quiet assessment room within the Clinical Research Facility at St Thomas' Hospital, London, UK. This provided a confidential environment and one which the participant was familiar with as all their previous assessments had been carried out in this room. Interviews were conducted by the CI and were audio recorded on two digital Dictaphones to ensure accuracy and preservation of the information in case there was a fault with one of the Dictaphones. The interviews were transcribed verbatim by the CI and checked for accuracy against the original recording. Participants were offered a copy of the transcript of the interview. A naturalism mode of transcription was used where the transcript matches as closely as possible the actual interview with every utterance recorded (Oliver, Serovich et al. 2005).

### **Statistical analysis**

Statistical analysis of the data was conducted using SPSS for windows version 22.0 (IBM Software, Hampshire, UK). A p-value of less than 0.05 was considered statistically significant. Standard distributional checks were made. For each of the outcome measures analysed, univariate descriptive statistics were summarised by randomised group to provide an overview of the data. Summary measures for the baseline characteristics of each group were presented as mean and standard deviation for continuous 'approximate' normally distributed

variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Univariate analyses were performed to compare study group using appropriate statistical tests according to the type and the distribution of the data: independent t-test or Mann-Whitney for continuous variables and chi squared or fisher's exact test for categorical variables. For clarity of the presentation, specific statistical analyses and power calculations for each investigation are presented within the related chapter.



**Chapter 6 : Reliability study- The  
intra- and inter-rater reliability of  
shoulder range of motion and  
strength**

### **Authors Contribution to this study**

Fiona Sandford designed this study. Hannah Dollings applied for ethical approval. Fiona Sandford and Hannah Dollings collected the data. Fiona Sandford analysed the data. Hannah Dollings was lead author on the publication discussing the strength results found in this chapter (Appendix 11:30). Fiona Sandford assisted in the writing and review process for this publication.

## **Introduction**

This study was carried out in order to investigate the intra-rater and inter-rater reliability of the chief investigator (Fiona Sandford) and co-investigator (Hannah Dollings) in the assessment of: shoulder range of motion (Flexion, abduction, external rotation and hand behind back) and shoulder strength (flexion, abduction, empty can position and full can position, internal and external rotation and elbow flexion). These impairment measurements form part of the secondary outcome measures in the main clinical study (Chapter 8). The investigation for the reliability of strength testing has been published (Dollings, Sandford et al. 2011) (Appendix 11.30).

## **Methods**

### **6.1.1 Design**

This study followed a non-experimental, two-examiner, within-subject, repeated measures design. Participants were assessed on one occasion only.

### **6.1.2 Participants**

This study was approved by the Biomedical & Health Sciences, Dentistry Sciences & Engineering Research Ethics Subcommittee at Kings College London (BDM/09/09-86) (Appendix 11.6). Participants were recruited by verbal invitation from Guy's Campus and friends and family. Inclusion criteria involved; anyone over the age of 18 years of age and with no history of shoulder pain. Exclusion criteria were: individuals under 18 years old, a history of shoulder pain, anyone with a history of shoulder pain, pregnancy and an inability to give informed consent. Any potential participant was excluded if they had shoulder pain on testing during the Neer sign and Hawkin's test, resisted external rotation, as well as palpation for pain around the region of the greater tuberosity (Lewis, Green et al. 2005, Lewis, Wright et al. 2005, Michener, Walsworth et al. 2009).

### **6.1.3 Measurements**

Full details of the measurements taken, positions and instruments can be found in Chapter 5.3.1. The range of motion measurements assessed in this study were: shoulder joint flexion, abduction, external rotation and hand behind back. Shoulder joint flexion and abduction were assessed using an inclinometer (Acuangle®, anglelevel) (Figure 5.1). The shoulder complex strength measurements assessed were; flexion, abduction, abduction in an empty and full can

position, internal and external rotation and elbow flexion and extension. The strength measurements were measured using a JTech PowerTrack™ II Commander hand-held dynamometer (Figure 5.2).

#### **6.1.4 Sample size calculation**

For a true reliability of 0.8 against an alternative reliability 0.9, based on a 5% level of significance and a power of 80% ( $\beta=20$ ), for two testers, it was calculated that 46 participants would be required (Walter, Eliasziw et al. 1998). Measurements were taken bilaterally on 23 participants who consented into the study, thereby making measurements on 46 shoulders.

#### **6.1.5 Data Analysis**

Intra and inter-rater reliability were calculated using intra-class correlation coefficients (ICC), 95% confidence intervals (95% CI), standard error of measurement (SEM) and the smallest detectable difference (SDD) (Portney and Watkins 2000). The mean value of the three measurements was used for each movement or strength test in order to calculate the intra and inter-rater reliability.

ICC values greater than 0.75, were considered to indicate good reliability and those greater than 0.91, indicative of excellent reliability (Portney and Watkins 2000). The 95% CI were calculated using ICC model 2,1. ICC model 2 was selected for use in the data analysis as it is considered to be the most appropriate to generalise the findings of the study using these methods of measurement to other clinicians with similar characteristics (Portney and Watkins 2000). The data was analysed using SPSS Version 22 (SPSS Inc, Chicago, IL, USA). The options of two way random and absolute agreement were selected when analysing using the SPSS programme.

## **Results**

Twenty-three asymptomatic participants were recruited into the study. Sixteen females (70%) and seven males (30%) with a mean age of 37 years (SD 35.4 years range 22 to 73 years). The mean height was 173.4cm (SD 17.7, range 163cm to 188cm). Mean weight was 69.9kg (SD 30.4kg, range 52kg to 95kg). Mean body mass index was 23.2 kg/m<sup>2</sup> (SD 7.1kg/m<sup>2</sup>, range 18.4kg/m<sup>2</sup> to 28.4 kg/m<sup>2</sup>). The majority of participants were employed (87%) and undertook some physical activity per week (82.6%). Twenty (87%) individuals were right-hand dominant. The participant demographics are presented in Table 6.1 below.

Table 6.1 Participant demographics

	Participants (n=23)
Age in years	33 (29-37)
Height (cm)	173.40 (17.7)
Weight (kg)	69.90 (30.4)
Body mass index (BMI) (kg/m <sup>2</sup> )	23.18 (7.1)
Occupation	Retired =3 (13%) Medical profession= 9 (39%) Desk based= 11 (48%)
Activity level	No regular activity= 4 (17%) Walk more than 45mins per day=6 (26%) CV activities 1-3 x/week= 7 (30%) CV activities 4x/week= 6 (26%)
Hand dominance	Right hand dominant= 20 (87%) Left hand dominant= 3 (13%)

Legend: Summary measures represent means (standard deviation), median (interquartile range) or numbers (percentages). CV=cardiovascular

#### 6.1.6 Strength measurements

The intra-rater (ICC 2,3) results for both testers were excellent for all tests, with the exception of left shoulder flexion (tester A, ICC 2,3=0.89), right shoulder flexion (tester B, ICC 2,3=0.90) and right shoulder full can test (tester A ICC2,3=0.90. The two SEM results ranged from 1.3kg (right empty can test) to 3.2kg (left shoulder flexion) for tester A and from 0.9kg (left empty can test) to 2.5kg (left elbow flexion and right shoulder flexion).

The inter-rater (ICC2,3) results for all measurements were excellent, with the exception of abduction (ICC 2,3 = 0.77/0.87 , right/left). The two SEM measurements ranged from 0.9kg (right empty can test) to 4.1kg (right elbow flexion).

Table 6.2 Mean strength measurements for each test, intra and inter rater reliability and SEM in kg, continued on next page.

STRENGTH MEASUREMENTS		Flexion (kg)		Abduction (kg)		Full can (kg)		Empty can (kg)		L e g e n d :  S E M = s t a n d a r d
	rater	Right	Left	Right	Left	Right	Left	Right	Left	
Mean (SD) [range]		12.7 (4.3)	12.2 (4.4)	12.5 (3.4)	12.1 (3.7)	6.4 (3.2)	6.1 (3.6)	5.6 (2.4)	5.7 (2.6)	
		[6.3-25.2]	[6.6-24.6]	[7.2-22.2]	[5.6-25.5]	[2.5-15.6]	[2.6-15.5]	[2.3-11.5]	[2.0-9.8]	
Inter-rater reliability	AvsB	0.91	0.92	0.77	0.87	0.97	0.96	0.97	0.96	
ICC2,3 A vs B (95%CI)		(0.79, 0.96)	(0.87, 0.97)	(0.45, 0.91)	(0.63, 0.95)	(0.92, 0.99)	(0.92, 0.99)	(0.93, 0.99)	(0.92, 0.99)	
SEM (2SEM) (kg)		1.3 (2.6)	1.2 (2.3)	1.5 (3.1)	1.3 (2.6)	0.6 (1.3)	0.8 (1.5)	0.5 (0.9)	0.6 (1.2)	
Intra-rater reliability	A	0.97	0.89	0.94	0.94	0.9	0.96	0.94	0.93	
Rater A (95%CI)		(0.89, 0.98)	(0.62, 0.92)	(0.86, 0.98)	(0.86, 0.98)	(0.78, 0.96)	(0.85, 0.99)	(0.85, 0.98)	(0.83, 0.97)	
SEM (2SEM)(kg)		0.9 (1.7)	1.6 (3.1)	0.9 (1.7)	0.9 (1.9)	0.1 (2.0)	0.7 (1.4)	0.6 (1.2)	0.7 (1.4)	
Intra rater reliability	B	0.89	0.92	0.93	0.92	0.95	0.98	0.95	0.97	
Rater B ICC2,1(95%CI)		(0.75, 0.95)	(0.82, 0.97)	(0.85, 0.97)	(0.81, 0.97)	(0.88, 0.98)	(0.96, 0.99)	(0.88, 0.98)	(0.92, 0.99)	
SEM (2SEM)(kg)		1.2 (2.5)	1.2 (2.3)	0.8 (1.5)	1.0 (2.0)	0.7 (1.4)	0.5 (1.0)	0.7 (1.4)	0.5 (0.9)	

error of measurement, CI=95% confidence interval, SD=standard deviation. Inter-rater reliability calculated using ICC 2,3 and intra-rater reliability calculated using ICC 2,1.

STRENGTH MEASUREMENTS cont		External rotation (kg)		Internal rotation (kg)		Elbow flexion ( kg)	
	rater	Right	Left	Right	Left	Right	Left
Mean (SD) [range]		9.4 (3.5)	9.7 (3.7)	12.3 (5.0)	12.1 (5.6)	18.1 (6.9)	16.9 (7.1)
		[6.5-17.8]	[5.0-19.8]	[5.45-23.5]	[5.3-25.6]	[7.9-31.2]	[8.7-43.8]
	AvsB						
Inter-rater reliability ICC2,3		0.92	0.94	0.93	0.94	0.91	0.93
A vs B (95%CI)		(0.81 to 0.97)	(0.82 to 0.98)	(0.57 to 0.98)	(0.86 to 0.97)	(0.68 to 0.97)	(0.83 to 0.97)
SEM (2SEM) (kg)		1.0 (2.0)	1.0 (2.0)	1.3 (2.6)	1.5 (2.9)	2.1 (4.1)	2.0 (3.9)
	A						
Intra-rater reliability rater A		0.97	0.98	0.97	0.98	0.98	0.98
ICC 2,3(95%CI)		(0.93 to 0.99)	(0.96 to 0.99)	0.92 to 0.99	(0.96 to 0.99)	(0.96 to 0.99)	(0.97 to 0.99)
SEM (2SEM) (kg)		0.6 (1.2)	0.7 (1.3)	0.9 (1.7)	0.9 (1.9)	1.2 (2.3)	1.1 (2.2)
	B						
Intra-rater reliability rater B		0.96	0.95	0.98	0.97	0.98	0.96
ICC2,3(95%CI)		(0.90 to 0.98)	(0.87 to 0.98)	(0.97 to 0.99)	(0.94 to 0.99)	(0.94 to 0.99)	(0.91 to 0.98)
SEM (2S2SEM) (Kg)		0.7 (1.4)	0.8 (1.5)	0.7 (1.4)	0.9 (1.7)	0.8 (1.6)	1.3 (1.5)

Legend: SEM=standard error of measurement, CI=95% confidence interval, SD=standard deviation. Inter-rater reliability calculated using ICC 2,3 and intra-rater reliability calculated using ICC 2,1.

## **ROM measurement**

The intra-rater ICC (2,1) reliability measurements were found to be good to excellent for all ranges of motion measurements. With the exception of left hand behind back, which had excellent reliability (ICC 2,1=0.93), good reliability was found for the measurements of external rotation and hand behind back for both testers. Excellent reliability was demonstrated for all measurements of flexion and abduction by both testers, with the exception of right shoulder flexion (ICC 2,1 = 0.90). The two SEM measurements ranged from 8.2° (right shoulder flexion) to 9.2° (left shoulder abduction) for tester A and 4.0° (right shoulder flexion) to 13.6° (right shoulder abduction) for tester B. For hand behind back and external rotation two SEM results ranged from 2.8cm (right shoulder external rotation) to 4.3cm (left hand behind back). For tester A and 2.5cm (left hand behind back) to 4.6cm (right hand behind back) for tester B.

The inter-rater ICC 2,3 reliability results demonstrated good reliability other than those for flexion which demonstrated excellent reliability (ICC2,3= 0.91/0.92 right/left). The two SEM measurements ranged from 7.9° (left shoulder flexion) to 10.2° (right shoulder abduction) and 3.0cm (right shoulder external rotation) to 3.9cm (right hand behind back).



RANGE OF MOTION MEASUREMENTS		Flexion (degrees)		Abduction (degrees)		External rotation (cm)		Hand behind back (cm)	
	rater	Right	Left	Right	Left	Right	Left	Right	Left
Mean (SD) [range]		169.0 (13.7)	166.9 (14.0)	166.1 (12.8)	164.9 (12.2)	41.3 (4.3)	40.5 (5.2)	15.7 (4.9)	12.7 (4.5)
		[141.8, 202.0]	[145.0, 201.8]	[142.5, 196.5]	[145.5, 196.3]	[34.1, 51.0]	[31.8, 51.5]	[5.8, 22.8]	[4.5, 21.5]
Inter-rater reliability ICC2,3 A vs B (95%CI)	AvsB	0.91 (0.84, 0.96)	0.92 (1.87, 0.96)	0.84 (0.73, 0.92)	0.88 (0.79, 0.94)	0.88 (0.79, 0.94)	0.86 (0.75, 0.93)	0.84 (0.73, 0.92)	0.84 (0.73, 0.92)
SEM (2SEM)		4.2 (8.3)	4.0 (7.9)	5.1 (10.2)	4.2 (8.4)	1.5 (3.0)	2.0 (3.9)	2.0 (3.9)	1.8 (3.6)
Intra-rater reliability rater A (95%CI)	A	0.90 (0.70, 0.95)	0.91 (0.80, 0.96)	0.91 (0.81, 0.96)	0.91 (0.80, 0.96)	0.87 (0.72, 0.94)	0.85 (0.68, 0.93)	0.83 (0.65, 0.93)	0.77 (0.55, 0.90)
		4.6 (9.2)	4.3 (8.5)	4.3 (8.6)	4.1 (8.2)	1.4 (2.8)	2.0 (3.9)	2.0 (3.9)	2.1 (4.3)
SEM (2SEM)		2.0 (4.0)	3.9 (7.8)	6.8 (13.6)	2.6 (5.3)	1.5 (3.0)	1.7 (3.4)	2.3 (4.6)	1.2 (2.4)
Intra-rater reliability rater B ICC2,1(95%CI)	B	0.98 (0.96, 0.99)	0.92 (0.81, 0.96)	0.91 (0.79, 0.96)	0.94 (0.86, 0.97)	0.90 (0.78, 0.96)	0.90 (0.79, 0.96)	0.80 (0.59, 0.91)	0.93 (0.85, 0.97)
		2.0 (4.0)	3.9 (7.8)	6.8 (13.6)	2.6 (5.3)	1.5 (3.0)	1.7 (3.4)	2.3 (4.6)	1.2 (2.4)

Table 6.3 Mean range of motion for each test, intra and inter rater reliability and SEM in degrees or cm.

Legend: SEM=standard error of measurement, CI=95% confidence interval, SD=standard deviation. Inter-rater reliability calculated using ICC 2,3 and intra-rater reliability calculated using ICC 2,1

## Discussion

This reliability study examined the intra and inter-rater reliability of clinical methods for measuring both shoulder strength and range of motion. The methodologies used and described within this reliability study are simple to use and time efficient.

### 6.1.7 Strength measurement

The Jtech Power Track II Commander hand-held dynamometer was used together with a specific testing protocol to measure isometric muscle strength of particular shoulder muscle groups in asymptomatic participants performing 'make' tests. The measurement methodology of strength assessment utilised by the CI and the co-investigator demonstrated good inter-rater reliability ( $ICC_{2,3} \geq 0.77$ ) and intra-rater reliability ( $ICC_{2,1} \geq 0.89$ ) in pain and symptom free individuals.

The findings of the present study support those of other investigations examining the reliability of measuring shoulder strength using hand held dynamometers, with similar findings of greater reliability of intra-rater reliability than inter-rater reliability (Agre, Magness et al. 1987, Leggin, Neuman et al. 1996, Balogun, Powett et al. 1998, Hayes, Walton et al. 2002, Vermeulen, Bock et al. 2005). However differing methodologies, devices and research protocols make it difficult to make comparisons across studies.

### 6.1.8 Range of motion

The methods described utilised an inclinometer to measure shoulder flexion and abduction in degrees and a tape measure to assess shoulder external rotation range of motion and hand behind back in cm.

The measurement methodology of shoulder ROM measurement utilised by the CI and the co-investigator demonstrated good inter-rater ( $ICC_{2,1} \geq 0.89$ ) and intra-rater ( $ICC_{2,1} \geq 0.77$ ) reliability in pain and symptom free individuals. External rotation and hand behind back measurements were associated with poorer reliability than flexion and abduction. This is possibly due to the use of a tape measure and anatomical landmarks for the external rotation and hand behind back measurements which may have more potential for inaccuracy than with inclinometer placement. The measurement of hand behind back is cited in the literature as having poor reliability (Hayes, Walton et al. 2001, Edwards, Bostick et al. 2002, Hayes, Walton et al. 2002). However the intra and inter-rater reliability results of the measurement of hand

behind back were found to be similar to other studies (Green, Forbes et al. 1998) and much better than those found previously by Hayes et al (2001)  $ICC_{2,1}=0.39$  and Edwards et al (2002)  $ICC \leq 0.25$  for both intra and inter-rater reliability). Similar methodology was employed in all three studies (Green, Forbes et al. 1998, Hayes, Walton et al. 2001, Edwards, Bostick et al. 2002) and also in the present reliability study. However, Hayes et al (2001) and Green et al (1998) carried out their measurements in symptomatic patient populations. This is a potential reason for the differences in the reported outcomes. Despite the previously reported poor reliability hand behind back was selected as an outcome measure in this study and the main RCT due to its clinical utility and common restriction of range as a presenting feature in RC tendinopathy (Valentine and Lewis 2006). The American Academy of Orthopaedic Surgeons and Society of American Shoulder and Elbow Surgeons (Kumar and Satku 1994) also recommend the assessment of hand behind back due to its functional importance in so many activities of daily living. It is recognised that the measurement of hand behind back is not a valid measure of internal rotation of the shoulder (Mallon, Herring et al. 1996) and is subject to interference from pain and conditions located elsewhere in the upper limb (thumb, wrist and elbow) which might adversely affect the reliability of the measurement.

Both the intra and inter-rater reliability of shoulder abduction, flexion and external rotation measurements were found to be similar to previous studies measuring both symptomatic and asymptomatic participants when using similar methodologies (Valentine and Lewis 2006) and methodologies with differences such as lying down and plane of movement (Green, Buchbinder et al. 1998)

#### **6.1.9 Study limitations**

One limitation of this study is that the study participants were asymptomatic individuals with an average age of 33 (SD 35.4) years. Therefore generalisation of the results of this study to individuals of any other age range or a population of individuals with specific or generic shoulder symptoms is questionable.

Another limitation lies in the fact that the test, retest periods were short in duration. The consistency in the mean strength between measurements would indicate that fatigue was not an issue within the study but there may have been a learning effect present. This is relevant as the tests within each sequence were carried out in a standardised order (Portney and Watkins 2000). Testing over a period of days might have been preferable but was not possible within the time constraints of this reliability study. It could also be argued that any differences found

between values tested over days may have been due to participant related reasons rather than testing procedure.

## **Conclusion**

The findings of this study suggest, that;

- Using the methods employed in the population investigated in this study, and used as outcome measures in the main investigation demonstrate good to excellent intra and inter-rater reliability for the measurement of shoulder strength and range of motion.
- The SEM findings provide guidance for values that maybe considered as a real change in strength and range of motion.
- Further research is required to determine the intra- and inter- tester reliability in symptomatic individuals.

**Chapter 7 : Shoulder pain and the use  
of nutritional supplements: A  
questionnaire based investigation**

### **Authors Contribution to this study**

Fiona Sandford designed the study, applied for ethical approval and formulated the questionnaire and contents of the booklet. Fiona Sandford ran the pilot of the questionnaire with focus groups and made the amendments. The questionnaires were sent to the participating departments either by Fiona Sandford or Jeremy Lewis or an administrator. The data was inputted into a spreadsheet by an administrator. The data was analysed by Fiona Sandford. The qualitative data was coded and themed by Fiona Sandford and then discussed with Jeremy Lewis until agreement was reached.

## Introduction

The printed press (Griffiths 2014, O'Connor 2015) and social media (e.g. <http://www.webicina.com/nutrition>) increasingly focus on food, nutrition and health, and the conclusions reached in these communications may impact on the perceptions of wider the community including healthcare workers, patients and those wishing to prevent illness (Swinburn and Egger 2002). References to food and nutritional supplements are published regularly and an example is depicted in Figure 7.1.

Figure 7.1 An example of an article pertaining to nutritional supplements in the printed press



<http://metro.co.uk/2013/07/31/are-vitamin-supplements-really-the-answer-to-our-health-prayers-3904559/>

It is estimated that 35-40% of adults in the United Kingdom (UK) regularly use dietary supplements, making the annual UK market alone in 2012 an estimated £738 million (<http://www.euromonitor.com/vitamins-and-dietary-supplements-in-the-united-kingdom/report>).

There has been a steady increase in the use of dietary supplements for musculoskeletal conditions, such as glucosamine (Ostojic, Arsic et al. 2007), and polyunsaturated fatty acids (Maroon and Bost 2006). This is potentially supported by published research investigation that

have concluded significant benefit in taking nutritional supplements for a cohort of athletes with multiple tendinopathies (Mavrogenis, Johannessen et al. 2004). This investigation however was at a high risk of bias due to data analysis being conducted as an on-treatment (and not an intention-to-treat) basis, and non-compliers being excluded from data analysis. Supplement use in individuals with tendinopathy remains controversial and unregulated and lacks guidance from the findings of appropriately designed and controlled research investigations. These issues need to be addressed to understand better the relative benefit of nutritional supplements in those with tendinopathy. One step in this process is to determine how many people are taking supplements for shoulder pain, together with the reasons for taking as well as not taking supplements.

This study aimed to establish: the extent of use; beliefs surrounding use; and any perceived side effects of usage of supplements in people experiencing shoulder pain and supports the main randomised controlled trial (The efficacy of polyunsaturated fatty acids and exercise in the treatment of RC tendinopathy ISRCTN 17856844).

### **Aim of research:**

The objective was:

To evaluate the current use of self-prescribed dietary or nutritional supplements in a cohort of patients with shoulder pain.

The primary research questions for this chapter were:

- (i) How many people are taking supplements to aid their recovery from shoulder pain?
- (ii) What are the reasons for people with shoulder pain choosing to use or not to use nutritional supplements?

### **Design, setting and methods**

A descriptive survey methodology was employed using paper based questionnaire booklets (Appendix 11.12). Questionnaires are the most commonly used tool in survey research (Shaughnessy, Zechmeister et al. 2011) and it was felt that this was the best method available to collect the required data. A paper based questionnaire was selected to ensure ease of completion at the eight different research sites where on-line surveys might have been more difficult and introduced a bias in that only those proficient with computer use might have taken part. It also importantly allowed participants to feel under no obligation to participate



as it was their decision to return the questionnaire or not. This process also allowed the participants to complete the questionnaire in a place of their choice and taking as much time as they required.

#### **7.1.1 Sample size**

A sample of convenience was used from eight locations within the United Kingdom (UK). They were selected to represent a diversity of locations and healthcare settings (both public and private). In addition, the locations were selected due to the willingness of at least one member of the physiotherapy team at each site to act as the principal investigator at that site and take on local responsibility for the study.

A total of 325 questionnaire booklets were sent in batches of 50 booklets to each of the five participating National Health Service (NHS) site and in batches of 25 to the three participating private physiotherapy clinics. The difference in the number of questionnaires sent out was due to the estimated number of eligible patients who would be seen within that setting in the time frame given. This information was provided by the local investigators. The NHS sites had a higher volume of patients with shoulder pain being seen by the service and so had a larger potential recruitment pool from which to recruit.

#### **7.1.2 Ethical approval**

Ethical approval was granted from West London Research Ethics Committee three, National Research Ethics Service, Room 4W/12, 4<sup>th</sup> Floor West, Charring Cross Hospital, Fulham Palace Road, London W6 8RF on 12<sup>th</sup> July 2010 (REC re: 10/H0706/41) (Appendix 11.13). A principal investigator was identified at each site. Local Research and Development approval was sought and granted at each separate site prior to the study commencing at that site. Participants gave written informed consent (Appendix 11.11).

#### **7.1.3 Positionality of researcher**

The chief investigator (FS) was responsible for developing the research protocol, recruiting the clinical sites and ensuring local research and development ethical approval was granted, analysing the data and coding and generating the themes from the subjective data. Cross verification or researcher triangulation was achieved with a supervisor (JL) independently coding and analysing the subjective responses generated from the open questions and consensus being reached as to the themes and sub-themes.

#### **7.1.4 Study design**

The survey comprised of four sections: (i) the background of the participants, (ii) for those not taking supplements, their reasons and beliefs regarding supplements, (iii) for those taking supplements, their beliefs and reasons for doing so and (iv) the last section of the survey comprised of four patient reported outcome measures. These were;

1. Oxford Shoulder Score (OSS) (Dawson, Rogers et al. 2009)
2. Shoulder Pain and Disability Index (SPADI) (Breckenridge and McAuley 2011)
3. SF-36 (Ware and Sherbourne 1992)
4. Euro Qol EQ-D5 3L (Brooks 1996)

#### **7.1.5 Questionnaire design**

Individual questions were devised by the CI using the available literature on supplement use to shape topic areas. The questions were discussed and reviewed by JL (co-supervisor).

Once the initial survey was formulated, it was then peer reviewed by a focus group of nine physiotherapists at St Thomas' Hospital, London, UK who were working within upper limb rehabilitation. These physiotherapists independently reviewed the questionnaire. It was also piloted by ten patients who were attending the shoulder exercise class at the same hospital. The patients were approached and asked to read a questionnaire that would be used in a study. The ten patients who volunteered were a sample of convenience and were advised that completing or not completing the review of the questionnaire would not affect their treatment. All aspects of the survey were reviewed including; intelligibility, terminology, relevance and comprehensiveness. The feedback gained from the physiotherapists and patients informed the final content of the survey and questions were re-worded and altered as indicated. Terminology such as "nutritional" was highlighted as possibly being confusing and so terms such as these were altered and some questions re-worded to ensure clarity.

#### **7.1.6 Questionnaire content**

The initial questions of the questionnaire sought demographic information. These questions included the participant's age, gender, height, weight, ethnicity (participants were asked to select one of 19 choices), duration of shoulder pain in months (participants selected zero-six weeks, six weeks to three months or more than three months given), education level (none,

secondary, higher), type of employment (manual, non-manual or not sure) and ability to work with shoulder problem (yes or no).

Participants were then asked if they were currently taking supplements.

Those who said they were not taking supplements were asked to consider why they were not taking supplements and asked to tick the sentences in the box below that corresponded to their views.

I don't believe in taking food/nutritional supplements

There is no evidence/ scientific basis for taking them

I am scared of any side effects

I have tried them but they didn't help (what did you try?)

I would like to take them but they are too expensive

I would like to take them but I don't know what to take

I don't know what food/ nutritional supplements are

Anything else you think is relevant

Those participants who said they were taking supplements were directed to another set of questions which asked them to list the supplements they were taking. They were also asked to comment on and tick the statements in the box below, which best represented their views

Of these which ones if any are you taking for your shoulder pain

Any benefit for your shoulder pain?

Where did you first learn about these supplements?

Estimated monthly cost of the supplements you are taking for your shoulder

Would you recommend these supplements to others?

Any side effects?

Anything else?

#### **7.1.7 Participants and recruitment**

Patients seeking treatment for their shoulder pain were recruited from eight physiotherapy departments. Five National Health Service (NHS) sites and three private clinics, providing a sample that included; rural, coastal and inner city locations (both London and Nottingham). They were selected to give greater transferability of the findings to the population of the UK.

#### **7.1.8 Inclusion criteria:**

Patients suffering with shoulder pain of more than one month duration and over 16 years of age.

#### **7.1.9 Exclusion criteria:**

16 years of age or under

#### **7.1.10 Data collection**

The data collection methods are described in Chapter 5.

Potential participants with a diagnosis of shoulder pain were invited to participate in the study by their treating physiotherapist. Following the completion of a consent form they were then given the set of questionnaires in a booklet form (Appendix 11.12). Once the questionnaire was completed it was placed in a sealed envelope and returned to the physiotherapist. The completed anonymised questionnaires were returned by secure special delivery (Royal Mail) to JL (co-supervisor) at an NHS site. The booklets were then securely stored in a locked cabinet in a locked office.

#### **7.1.11 Data analysis**

Data was entered onto an excel spreadsheet and then transferred to SPSS for Windows version 22.0 (IBM Software, Hampshire, UK) by the CI (FS). For the open questions a thematic style of analysis was used to explore across the data set to identify repeating patterns of meaning. The data was read and re-read to aid familiarisation and then codes were generated using Nvivo V10 software (QSR International (UK) Ltd, London UK) by the CI (FS). The codes

were grouped and discussed between JL (co-supervisor) and the CI (FS), to produce agreed themes. Extracts from the questionnaires were chosen by the CI (FS) to demonstrate the themes.

Triangulation was achieved through the discussions between the researchers regarding codes, themes and analysis.

#### **7.1.12 Statistical analysis**

Both univariate and multivariate analyses were used to assess for associations between participant demographics and supplement use.

### **Findings and results**

261 out of a possible 325 questionnaires were returned representing an 80% return rate. No questionnaires had to be discarded due to being incomplete.

The demographic characteristics are detailed in Table 7.2. The level of disability reported by the respondents as measured by the OSS and SPADI lies in the 'moderate' category and is similar to other studies on shoulder pain (Ekeberg, Bautz-Holter et al. 2010, Younis, Sultan et al. 2011). There were more female respondents than male at a ratio of approximately 1.6:1 (female: male). The majority of the sample was white (94%). The average body mass index was above the desirable 'healthy' range (18.5-24.9kg/m<sup>2</sup>) (WHO 1998). Approximately 45% of respondents reported to be unable to work due to their shoulder pain and the majority (79%) had experienced shoulder pain for more than three months.

Table 7.1 Demographic characteristics of respondents

Variable		Value
Gender	Female	162 (62%)
Age in years (SD)		50 (16.5)
Body mass index (kgm <sup>-2</sup> )		27 (5.9)
Ethnicity	Not stated	3 (1.1%)
	Asian	7 (2.7%)
	Black	3 (1.1%)
	Mixed	3 (1.1%)
	White	246 (94.3%)
Type of practice	NHS	200 (76.6%)
	Private	61 (24.4%)
Education	Higher	113 (43.3%)
	Secondary	68 (26.1%)
	None	3 (1.1%)
	No response	77 (29.5%)
Employment	Full time	123 (47.1%)
	Part time	42 (16.1%)
	Homemaker	7 (2.7%)
	Retired	63 (24.1%)
	Unemployed	9 (3.4%)
	No response	17 (6.5%)
Type of work	Manual	84 (32.2%)
	Non-manual	95 (36.4%)

	Not sure	3 (1.1%)
	No response	79 (30.3%)
Number unable to work due to shoulder pain	No response	30 (11.5%)
		117 (44.8%)
Duration of shoulder pain	0-6 weeks	10 (3.8%)
	6 weeks- 3 months	29 (11.1%)
	More than 3 months	207 (79.3%)
	No response	15 (5.7%)
Oxford shoulder score		31 (10.4)
0-48 48=highest		
SPADI		45 (25.3) <sup>†</sup>
0-100; 100=highest		
EQ-5D		0.69 (0.59-0.80) <sup>†</sup>
-0.5-1.0; 1=highest		
EQ-5D health quality VAS		69 (24.1)
0-100; 100=highest		
SF36 mental component summary		46 (16.2)
0-100; 100=highest		
SF36 physical component summary 0-100; 100=highest		37 (14.0)

Legend: SF36 =short form 36 item quality of life questionnaire, Summary values are given as mean and (standard deviation) other than when represented by<sup>†</sup> and the median and (interquartile range) is given.

The numbers of respondents taking supplements for any condition or reason was 100 (38%). Of these 100 respondents, 82 reported taking supplements to help them with their shoulder pain.

Table 7.2 Supplement use within this cohort

	Information for those taking supplements	Information from the whole cohort
<b>N</b>	100 (38%)	261 (100%)
<b>Taking supplements for shoulder pain</b>	82/100 (82%)	82/261 (31%)
<b>Taking omega 3 or cod liver oil for shoulder pain</b>	52/100 (52%)	52/261 (20%)

Legend n=number, numbers and percentages presented

The reasons given by the 161 respondents not taking supplements were varied citing different themes, and are detailed in table 7.3.

Fifty per cent of respondents stated their reasons for not taking supplements were either '*I don't believe in them or there is no scientific basis*'. The other most regularly cited reason was that participants would like to take them but did not know what to take.

Table 7.3 The reasons given by respondents for not taking supplements

<b>Reason</b>	<b>n=161</b>
There is no evidence/scientific basis for taking them	33 (20.5%)
I don't believe in taking food/ nutritional supplements	50 (31.1%)
I am scared of any side effects	11 (6.8%)
I have tried them but they didn't help	27 (16.8%)
I would like to take them but they are too expensive	31 (19.3%)
I would like to take them but I don't know what to take	51 (31.7%)
I don't know what food/nutritional supplements are	12 (7.5%)

Legend n=number. Numbers and (percentages) presented.



Of the 82 respondents who reported they were taking the supplements to aid with their shoulder pain, 80% felt that they were having no or minimal benefit. This is further supported by 50% reporting they would not recommend or would be unsure about recommending them to others. The estimated monthly cost of the supplements being taken for shoulder pain ranged from £0.30 to £48.00 with the median value being £5.50. The figures are detailed in Table 7.4 on the next page.

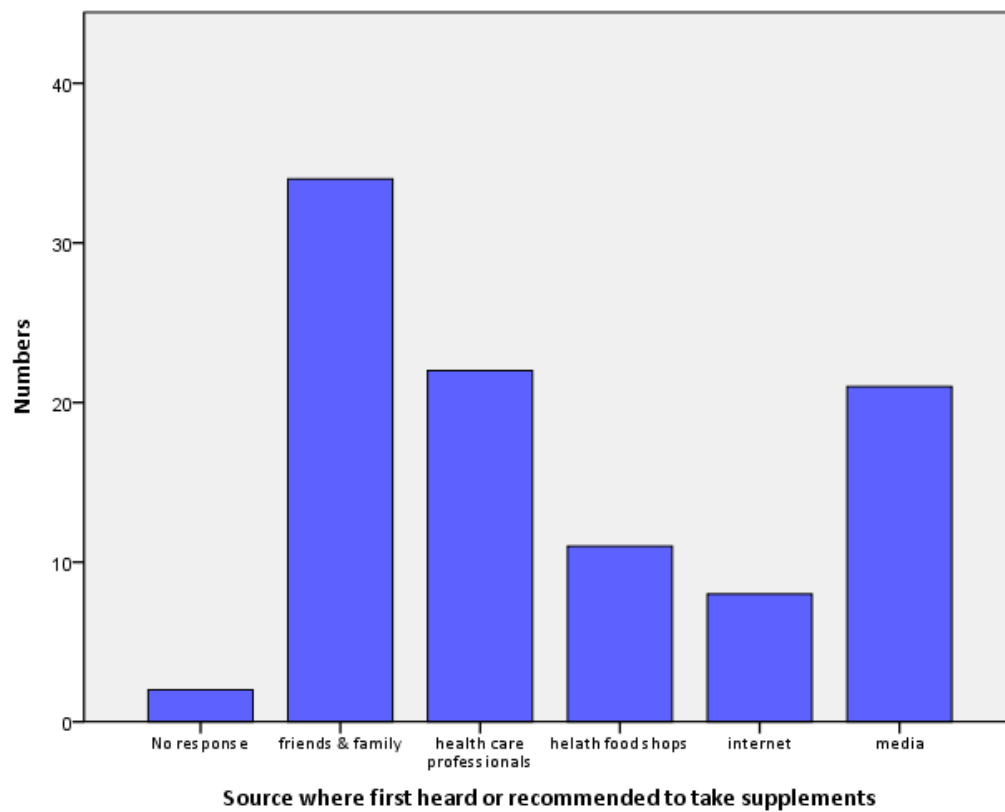
Table 7.4 Perceptions regarding supplement use from those who reported taking them

Are the supplements you are taking for your shoulder having any benefit on your pain	None	41/82 (50%)
	Minimal	25/82 (30.5%)
	Good	8/82 (9.9%)
	Very good	4/82 (4.9%)
	Excellent	4/82 (4.9%)
	Don't know	6/82 (7.4%)
Estimated monthly cost	£5.50†	Range (0.30-48.00)
Would you recommend these supplements to others	No	8/82 (9.8%)
	Unsure	33/82 (40.2%)
	Yes	39/82 (47.6%)
	No response	2/82 (2.4%)

Legend: Actual numbers and percentages given other than †which denotes median value and range

Respondents reported first learning of their supplements through a variety of means (Figure 7.2) with the largest percentage being from friends and family (34%), followed equally by health care professionals (22%) and media (21%).

Figure 7.2 Bar chart showing where participants first learnt about the supplements they are taking.



A wide variety of supplements were listed as being taken to aid with shoulder pain and these can be seen in Table 7.5 along with the median daily dose consumed.

Table 7.5 Supplements listed as being taken for shoulder pain

Supplement	Number of times listed	Median daily dose in mg (interquartile range)	Daily dose range in mg
Rosehip	2	4500 (4000-4500 50 <sup>th</sup> percentile)	4000-4500
Glucosamine	31	500 (500-1000)	100 – 1500
Chondroitin	11	400 (400-500)	100- 1000
Cod liver oil	35	525 (500-1000)	120-1000
Omega 3	24	1000 (510-1000)	75-2500
Flax seed oil	2	7000	7000
Multi vitamins	5	450 (70-500)	50-800
Apple cider vinegar	1	15 ml	15 ml
Devils claw extract	2	Mean=482.50 (SD=60.10)	440-525
Vitamin D	3	62.50 (13.75 – 325)	10-400
Vitamin C	3	1000 (300-1000)	60-1000
Calcium	3	500 (140-1500)	30-1500
Methylsulfonymethane	1	1000	1000
Hyaluronic acid	1	750	750

Legend: Median values and interquartile ranges given other than when mean is stated and mean values are given with SD= standard deviation

Of the 59 respondents who reported taking fish oil (omega 3 PUFAs and cod-liver oil) for their shoulder pain, the dose of fish oils taken is detailed in Table 7.6.

Table 7.6 Reported intakes of oil and intakes of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in 59 respondents who reported consuming fish oil supplements

<b>Supplement</b>	<b>Oil g/wk</b>	<b>Range g/wk</b>	<b>EPA g/wk</b>	<b>DHA g/wk</b>
Cod Liver Oil (n=35)	3.68 (3.5,7.0)	0.84-45.5	0.40 (0.38,0.76)	0.31 (0.29, 0.58)
Omega 3 (n=24)	7.0 (3.58- 7.0)	0.53 – 17.5	1.26 (0.64, 1.26)	0.84 (0.43, 0.84)
Flax oil (n=1)	49000	N/A		

Legend: Data are median values with interquartile ranges /wk= per week, n= number

Table 7.7 Unadjusted associations between taking supplements and demographic factors

Variable	Taking supplements		P value
	Yes	No	
<b>N=82</b>			
Age in years (SD)	54 (17.0)	47 (15.7)	0.0015*
Female gender	69 (69%)	93 (58%)	0.069
Male gender	31 (31%)	68 (42%)	0.069
White ethnicity	96 (96%)	151 (94%)	0.576
Higher education	42 (64%)	71 (60%)	0.739
Employed	54 (58%)	111 (73%)	0.019*
Non-manual work	37 (63%)	58 (47%)	0.049*
Duration >3 months	80 (86%)	127 (83%)	0.530
Private	23 (23%)	38 (24%)	0.911
NHS	77 (77%)	123 (76%)	0.911
BMI	27 (5.1)	27 (6.3)	0.9232
OSS	30 (9.9)	31 (10.8)	0.4846
SPADI	24 (43-68)	22 (42-65)	0.4313
SF36 PCS	37.6 (14.02)	38.46 (14.62)	0.108
SF36 MCS	47.24 (15.46)	45.61 (16.71)	0.432
EQ5D	0.69 [0.52-0.76]	0.73 [0.59-0.80]	0.168
EQ 5D Health status	68.39 (21.62)	69(25.58)	0.844

Legend: Summary measures are represented as means (standard deviation) and numbers (percentages). NHS= National Health service, BMI= body mass index, OSS= Oxford Shoulder Score, SPADI= Shoulder pain and disability index SF36 PCS= short form 36 physical component score, SF36 MCS= short form 36 mental component score, EQ 5D= Euro Qol 5D

Associations were examined using univariate analysis, other than ED 5D where median and IQR are presented and a Mann Whitney test was used. \*represents a statistically meaningful association.

The data were examined to see if there were any associations between demographic variables and taking supplements. Positive associations were found between supplement taking and age (the older the participant the more likely they were to take supplements), employment and non-manual work (Table 7.7).

Following multivariate analysis of the data, only the female gender and age remained significantly associated with supplement use. Being female was strongly associated with over 2-fold higher taking supplements as compared to males (Adjusted odds ratio: 2.2, 95% CI = [1.05-4.61];  $p=0.04$ ). A 2% increase in uptake was observed for every additional year in age (adjusted odds ratio: 1.0, 95%CI = [0.99-1.05];  $p=0.05$ ).

#### **7.1.13 Subjective information from questionnaire**

Several themes were highlighted within the open questions and free text sections of the questionnaires. These related to reasons for taking or not taking supplements.

##### **7.1.13.1 Balanced diet:**

The importance participants place on a balanced diet was high, with some expressing the fact their diet is well balanced and healthy would mean that nutritional supplements were not required.

*"I believe good nutrition is important and I'm unsure about food supplements."* Participant 22.

*"It's all a load of old tosh if you ask me. Nutritional supplements can't be worth it if you have a balanced diet."* Participant 56.

*"I have a healthy diet so don't feel I need to take supplements."* Participant 98.

*"I have previously taken supplements for body building but not for eight years. Since then I have found a balanced diet is more sustainable and easier on digestion."* Participant 225.

*"I think people should be able to get most of the nutrients needed from a balanced diet."*

Participant 109. This participant, who held the belief that most nutrients should be available from a balanced diet, was also taking evening primrose, cod-liver oil and vitamin B12. This demonstrates that this belief was held by both those who were taking supplements and those who were not. This is a view which is also held by some health professionals working in the speciality of Nutrition (Sanders 2014). Frequently repeated messages from the government

and NHS recommending and highlighting the benefits of a balanced diet are likely to have had an influence on the participant's beliefs (NHS)

(<http://www.nhs.uk/livewell/5aday/pages/5adayhome.aspx>).

Others felt that because their diet was lacking in a particular area e.g. poor fish intake or if they'd had a particular day where their diet was poorer then they might take supplements to 'compensate' for this perceived deficiency.

*"Most things you can get from a balanced diet. The only reason I take supplements is because I do not eat much fish."* This statement was made by Participant 78 who reported taking cod liver oil for their shoulder pain.

Other drivers cited for taking supplements were the perceived benefits that participants felt they experienced from taking the supplements.

*"My shoulder can be more painful on days I don't take a tablet [Cod liver oil]."* Participant 42.  
*"As each additional supplement was taken the benefit seemed to increase."* This statement was made by Participant 132 who was taking glucosamine, methyl sulfonylmethanemethone, marine chondroitin sulphate, devils claw extract, and hyaluronic acid for shoulder pain.

*"It's difficult to tell any direct effect, but I tend to feel that things might well be worse i.e. more general stiffness if I didn't take them."* This statement was made by Participant 131 who reported taking glucosamine for shoulder pain. This echoes the sentiment that participants reported that often supplements were used to prevent colds or joint problems rather than to treat symptoms which were already present.

*"They [glucosamine and chondroitin] are used for prevention more than pain relief."* Participant 79.

There was a belief that supplements would aid in the recovery from shoulder pain,  
*"I believe the fish oil will assist in muscle recovery."* Participant 246.

Others reported that whilst they believed that supplements worked for other conditions they doubted that they would work for their shoulder pain;



*"Don't see any harm in the things but I question for this [shoulder pain] use."* Participant 115.  
*"I do believe that food/nutritional supplements can be effective for some conditions but not specifically for my shoulder pain."* Participant 231.

Respondents also described the lack of perceived benefit when they had previously taken supplements which led to them stopping.

*"Used to take glucosamine/chondroitin but too expensive so I stopped and felt no difference at all."* Participant 170.

*"Because these supplements take months to start working and I forget to take them I have never felt any benefit from their use."* Participant 166.

*"I have tried things like cod-liver oil when I had inflammatory arthritis in my teens but unsure if this helped or not so do not take any longer."* Participant 212.

*"I have tried some intermittently but often motivation wanes as I'm unsure whether they work."* Participant 232.

This reduction in motivation when a supplement does not have obvious immediate benefits is a key point and links into the importance of perceived benefit of a treatment and adherence. Evidence suggests that people are more likely to adhere to a treatment if they believe that it is beneficial (van den Bemt, Zwikker et al. 2012, Sjolander, Eriksson et al. 2013, Venkatachalam, Abrahm et al. 2015). This was a predominant theme found in the qualitative study (Chapter 9).

Several participants reported forgetfulness and memory as a reason for not taking supplements. This was also highlighted in the interview responses of the participants in the main RCT and presented in Chapter 9.

*"I forget to take them."* Participant 247.

Some respondents reported side effects or the potential for side effects as reasons for not taking supplements. A few cited bowel habits or upset stomach whilst previously taking a variety of supplement.

*"Glucosamine upsets my stomach."* Participant 186.

The physical factors of taste and size of capsules or tablets were also highlighted as barriers to taking supplements and this is echoed again in the exploring attitudes study (Chapter 9).

*"Started to take Glucosamine but too large to swallow."* Participant 165.

*"I did not like the taste of cod liver oil. I am worried if I take supplements I will put on weight."*

Participant 100. This participant highlights concerns regarding the possible unwanted side effects of taking a supplement. The perceived potential benefit for this participant did not outweigh the potential disadvantage or risk she perceived.

Surprisingly only one participant mentioned any potential negative health side effects which have been reported in the press and media from taking nutritional supplements.

*"Even supplements of vitamins and minerals found in the diet can be unhealthy in large amounts (e.g. fat soluble vitamins)."* Participant 47.

#### **7.1.13.2 Marketing and evidence**

The theme of over exaggerated claims and lack of regulation as well as the perception of the lack of scientific evidence supporting their use was regularly highlighted in the subjective comments repeatedly by respondents.

*"I think about taking them but they seem to make extravagant claims which I don't believe."*

Participant 37.

*"I'm largely unconvinced by the arm of half science shouted out in adverts for them."*

Participant 115.

This issue of aggressive marketing was raised several times,

*"On the whole I think they are a waste of money. They are heavily marketed and poorly regulated."* Participant 47.

There is publicity in the media regarding nutritional supplements (Greiner, Clegg Smith et al. 2010). With news articles highlighting their benefit for a wide range of conditions and it's likely that that this widespread almost daily exposure to these reports might influence the wider population and their interest in the use of nutritional supplements (Rahmawaty, Charlton et al. 2013). This can also be seen in the number of participants (29%) reporting that it was through the media or press and internet that they first learnt about the particular supplements they were taking.

Several respondents reported that they had *“never considered it.”* Participant 144 or *“Honestly never given them a thought, never had it suggested, never tried them.”* Participant 257. This was coupled with some reporting whilst they had heard of supplements they, *“don’t know which ones to take.”* Participant 39.

Finally, the financial burden of supplement taking was mentioned by some as a barrier.

*“Don’t fancy spending money.”* Participant 257.

*“On the whole I think they are a waste of money.”* Participant 47.

Respondents also discussed the physical burden of taking more pills that the participant perceived as *“unnecessary”* as a reason for them not taking supplements,

*“I am taking eight tablets per day. I don’t need any more (unnecessary) plus pain killers.”*

Participant 258.

## **Discussion of results**

This study aimed to evaluate the current use of self-prescribed dietary or nutritional supplements in a cohort of patients with shoulder pain and the results provide valuable information regarding supplement use in this cohort of patients. Thirty eight percent of the sample reported taking supplements. This is in concordance with the 35-40% range found in other larger scale surveys within the UK (Mason 2007)(<http://www.euromonitor.com/>). Of those who reported taking supplements, 82% reported taking them in part to aid their recovery of their shoulder pain. Just over half of those taking supplements were taking fish oils for their shoulder pain. The questionnaire design did not capture information as to whether those taking supplements started taking supplements after developing shoulder pain or whether they were taking them previously. This limitation needs to be addressed in future research. Some participants highlighted in the comments or open questions that they had been taking supplements previously, but that they felt that the supplements were helping with their shoulder pain. Interestingly, when asked if they would recommend these supplements to others, 50% were unsure or said no and only 20% reported that they felt the supplements they were taking had a good/very good or excellent effect on their shoulder pain. This in part may be due to the supplements being taken having limited efficacy in shoulder pain and the doses at which they were being taken largely being sub-therapeutic doses. This will be further explored in the next section.

#### **7.1.14 Dietary supplements used**

Table 7.19 details the supplements that were listed as being taken and the scientific justification or rationale for their use in shoulder pain.

The weekly intake of the long-chain omega-3 polyunsaturated fatty acids in grams was calculated from the data to ascertain if an anti-inflammatory effect might have elicited at the doses stated. A weekly intake of 7.00g of omega 3 fish oil would equate to a weekly dose of 1.26g EPA and 0.84g DHA. This is calculated using the reference values that 1.00g of long-chain omega-3 fish oils contains on average 0.18g EPA and 0.12g DHA (Schuchardt and Hahn 2013). This is a sub therapeutic dose and as such would not be expected to provide any anti-inflammatory action. A daily intake in excess of 2.00g of EPA and DHA combined is widely considered to be required to elicit any anti-inflammatory effects (Calder 2011). Similarly an intake of 3.68g of cod liver oil per week would also be considered as a sub-therapeutic dose. An intake of 3.68g of cod liver oil would equate to 0.40g/wk of EPA and 0.30g/wk of DHA. This is calculated using the reference values that a one a day capsule contains on average 0.50g of cod liver oil. The EPA content is 10.3g/100g and the DHA content is 8.3g/100g, therefore a one a day capsule would provide 0.05g EPA and 0.04g DHA (MAFF 1998). This is well below the 14.00g recommend weekly intake of EPA and DHA to elicit an anti-inflammatory response (Calder 2011). However, a typical cod-liver oil capsule provides 5 µg vitamin D3 which is a significant intake (100% RDA for food labelling purposes).

Table 7.8 Supplements taken for shoulder pain listed by respondents and evidence to support their use.

Supplement	Evidence to support	References
Rosehip	Metal analysis of three RCTs (287 patients and a median trial-duration of 3 months)-looking at osteoarthritis (OA) all supported by the manufacturer showed a reduction in pain scores in rosehip powder group (145 patients) compared to placebo (142 patients) in patients with osteoarthritis: effect size of 0.37 [95% confidence interval (CI): 0.13-0.60], P=0.002.	(Cohen 2012)  (Christensen, Bartels et al. 2008)
Glucosamine sulphate & Chondriotin sulphate	Cochrane review concludes that there is evidence to support the use of glucosamine sulphate and chondriotin sulphate in combination to reduce pain.  3 animal studies	(Towheed, Anastassiades et al. 2001, Towheed, Maxwell et al. 2005)
Cod liver oil & omega-3 PUFAs	The evidence for their efficacy has been reviewed previously in chapter 4.	
Flax seed oil	Flax seed oil is Flaxseed oil contains 53% 18:3 Omega-3 fatty acids (mostly ALA) and 13% 18:2 Omega-6 fatty acids and so would provide some of the anti-inflammatory effects (although to a lesser degree due to the conversion from ALA as EPA and DHA)	(Kaithwas, Mukherjee et al. 2011)
Multi vitamins	No evidence found to support its use in tendinopathy	
Apple cider vinegar	No evidence found to support its use in tendinopathy	

Devils claw extract	Inconclusive evidence regarding whether it works or whether it is safe for use in OA  Some evidence to suggest devil's claw extract has a synergistic action with morphine in neuropathic rats.	(Brien, Lewith et al. 2006)  (Parenti, Arico et al. 2015)
Vitamin D	Low serum vitamin D levels were not found to be related to tear size or the degree of fatty infiltration in RC muscles. Vitamin D levels also had no correlation with functional outcomes post arthroscopic repair. Results are suggestive that vitamin D levels are not a risk factor for severity of a RC tear or for healing post repair.	(Angeline, Ma et al. 2014, Ryu, Kim et al. 2015)
Vitamin C	Only evidence found from an animal study: injected high dose vitamin c into a surgically cut Achilles rat tendon showed improved healing response in the earlier signs of angiogenesis and collagen synthesis..	(Omeroglu, Peker et al. 2009)
Calcium	No evidence found to support its use in tendinopathy	
Methylsulfonylmethane	Inconclusive evidence when used post operatively with a combination of other supplements. Inconclusive evidence to support its use in OA.	(Brien, Prescott et al. 2011, Gumina, Passaretti et al. 2012, Notarnicola, Pesce et al. 2012)
Hyaluronic acid	Evidence available for the use of inject able Hyaluronic acid but not oral supplementation	

Legend: RCT= Randomised controlled trial; ALA=Alpha linolenic acid; PUFAs= Polyunsaturated fatty acids; EPA= Eicosapentanaeic acid; DHA= Docosahexaenoic acid; OA= Osteoarthritis; RC= Rotator cuff.

Of the supplements listed as being taken (Table 7.10) to aid with shoulder pain the four most commonly reported were; (i) cod liver oil (67.3%, 35/52), (ii) glucosamine sulphate (59.6%, 31/52) and (iii) chondroitin (21.2%, 11/52) (often taken in combination) and (iv) Omega 3 PUFA (46.2%, 24/52). This is a similar finding to another much larger study of 25,639 men and women as part of The European Prospective Investigation into Cancer (EPIC) where the most commonly used supplement was also found to be cod liver oil (Lentjes, Welch et al. 2014). It is probable that the extensive use of cod liver oil originates from its historical use. Cod liver oil has been used for centuries to treat a variety of ailments from rheumatism to rickets (Rajakumar 2003). By the second world war the therapeutic benefits of cod liver oil were well recognised and it was routinely given to children to prevent rickets due to its relatively high vitamin D content (Rajakumar 2003). The mean age in this study was 50 years and these would be the children of the children of the pre and post war years and so it is probable that they were introduced to the benefits of cod liver oil through their family and this has been handed down from generation to generation. This is mirrored in the fact that it was recommendations from friends and family which ranked the highest amongst all sources of learning about supplements. A retail study (Mintel Report 2012) found that personal recommendation also carried the greatest weight influencing supplement use (Richmond 2012).

Glucosamine ranked the second most commonly used supplement in the questionnaire and was often taken with chondroitin. There are two types of glucosamine commonly taken for osteoarthritis; glucosamine sulphate (also known as the Rotta preparation of glucosamine) and glucosamine hydrochloride. Within the study results only two respondents reported they were taking specifically glucosamine sulphate.

Two Cochrane reviews have demonstrated that glucosamine (in the form of glucosamine sulphate) and Chondroitin effectively reduce pain and promote restoration of healthy joint tissue in individuals with osteoarthritis (Towheed, Anastassiades et al. 2001, Towheed, Maxwell et al. 2005). The Cochrane review in 2001 concluded that whilst there was evidence to support the use of glucosamine sulphate in osteoarthritis these findings could not be used to support the efficacy of different preparations of glucosamine by different manufacturers (Towheed, Anastassiades et al. 2001). Importantly, the Cochrane review in 2005 found that the pooled results for pain and function outcomes in those RCTs in which glucosamine hydrochloride was compared to placebo did not reach statistical significance (Towheed,

Maxwell et al. 2005). A meta-analysis, which has been frequently cited, included ten published trials investigating the efficacy of glucosamine and chondroitin for osteoarthritis of the hip and knee concluded that when compared to a placebo, glucosamine, chondroitin and a combination of the two do not reduce pain or improve joint space narrowing (Wandel, Juni et al. 2010). However, half the trials that were included in this analysis used glucosamine hydrochloride, and these trials showed no benefit. The other five trials investigated glucosamine sulphate and did show a benefit. When the results of the 10 trials were combined the significance showed in the glucosamine sulphate trials was diluted and thus the conclusion that glucosamine and chondroitin gave no added benefit over a placebo in osteoarthritis was potentially made erroneously. The type of glucosamine (hydrochloride or sulphate) is therefore critical when considering the research and for patient use.

This target population of the current survey study was general shoulder pain and so it is possible that the diagnoses of some of the participants might have been shoulder osteoarthritis. For this there is evidence of adequate quality to support the use of glucosamine sulphate. Three animal studies have investigated the efficacy of glucosamine on the healing of surgical tendon repairs (Oryan, Moshiri et al. 2011, Ozer, Taskesen et al. 2011, Taskesen, Ataoglu et al. 2015) results are only preliminary but suggest enhanced maturation of the tenoblasts and stimulation of collagen synthesis. This may warrant further investigation. The animal studies mimicked a surgical repair procedure rather than tendinopathy. No evidence could be found to support the use of glucosamine (sulphate or hydrochloride) in the treatment of tendinopathies.

#### **7.1.15 Sources influencing supplement use**

As previously discussed, friends and family ranked first in the responses to “Where did you first learn about these supplements?”

The influence of the media and internet when considering supplement intake is widespread as indicated by the results of this questionnaire study with 29% of respondents taking supplements reporting that it was through the media or internet that they first learnt of the supplements. These findings are in agreement with those of another questionnaire study where participants described the powerful positive influence the media (books and magazines) on an individual’s decision to use dietary supplements (Conner, Kirk et al. 2001).



The influence of health care practitioners (including doctors, physiotherapist, pharmacists and dieticians) ranked third.

#### **7.1.16 Industry regulation and quality of evidence**

Dietary supplements are covered by food law not by that pertaining to medicines. Explicit claims about the treatment or prevention of diseases or disorders are prohibited. However, health claims are permitted under the provisions of the European Union Health Claims Regulation (EC No 1924/2006) which came into force in 2007 and applies to all member states. The list of authorised health claims is under article 13 of the regulation which came into force at the end of 2014. In addition, some supplements/foods are covered by the European Framework Directive on Foods for Particular Nutritional uses (also called 'PARNUTs foods') which was first introduced in 1989, amended in 1999 and updated in 2009. It covers a range of products such as meal replacements, gluten free products and infant formulas. The basic tenets of food law is that it is illegal to sell food that is injurious to health or is not of the nature, substance and quality demanded and this provides the consumer with protection and peace of mind.

However, unlike drugs, foods have no required specification of formulation. The components must all be of food quality and any additives must be on the permitted list and the ingredients lists must be given in decreasing order. Without central standardisation of the individual ingredients within supplements it is left to the individual manufacturers to regulate (FDA 2014). This lack of central standardisation of the supplements was highlighted in some of the respondents' comments. There is a move towards greater regulation of the industry which it is hoped will lead to better protection and education for the consumer and hopefully necessitate well designed research trials investigating the efficacy of nutritional supplements. Two areas of legislation that have been introduced in the last decade have had a significant impact on nutritional and health messaging on foods and nutritional supplements within the European Union (EU). The first piece of legislation was the Directive 2002/46/EC whose aim is to protect consumers against potential health risks from foods and nutritional supplements and to ensure that consumers are not provided with misleading information. The introduction of the Health Claims regulation (EC1924/2006) by the European parliament ensured that any manufacturer making nutritional or health claims must comply with this legislation. Food labelling is covered by separate legislation. At the time of undertaking this study, those wishing to provide nutritional information on a label had to do so in accordance with the

provision of the food information to consumers Regulation (EU) 1169/2011. However new mandatory nutrition labelling has been introduced Regulation (EU) 1169/2011 and will become enforced by December 2016. This regulation combines two earlier directives (90/496/EEC – Nutrition labelling for foodstuffs and 2000/13/EC – labelling, presentation and advertising of foodstuffs).

Despite this lack of standardisation of dietary supplements, in one survey of 118 patients from general practices in Calgary, Canada, 68% of respondents stated that they felt that supplements were safer than prescription medication (Durante, Whitmore et al. 2001).

Associated with this lack of industry regulation with regard to implied health claims is the perception that the scientific evidence for the claims that are being made by the manufacturers is inadequate to support their use. With respect to the current survey, 20% of respondents who were not taking supplements felt that there was insufficient evidence to support their use. The questionable quality of evidence available was alluded to by one participant calling the evidence “half arm science”. The table detailing the evidence to support the use of the supplements listed (Table 7.8) illustrates the paucity of evidence currently available for the use of these supplements for shoulder pain.

#### **7.1.17 Sociodemographic drivers**

In terms of associations or drivers to supplement use, the only demographic variables which were found to be strongly associated to taking supplements were female gender and age. The positive association between female gender and supplement use is one commonly found within the literature (Conner, Kirk et al. 2001, Durante, Whitmore et al. 2001, Beitz, Mensink et al. 2004, Cox, Koster et al. 2004, Timbo, Ross et al. 2006, Pillitteri, Shiffman et al. 2008, van der Horst and Siegrist 2011). Increasing age is also considered as a common driver to supplement use (Conner, Kirk et al. 2001). Other factors which have been found on previous studies such as educational level, and employment status (MacLennan, Wilson et al. 2002) were not found to be associated with increased supplement use within this study.

The level of disability as measured by the OSS, mean= 31 (SD=10.4) and the SPADI , mean=45 (25.3) indicated a mild to moderate level of disability from their shoulder pain (Dawson, Fitzpatrick et al. 1996). It is interesting that level of disability was not found to be associated with supplement intake. Whilst there was no association found in this study it is commonly

reported finding those with better health or less disease severity have a greater supplement intake (Dickinson and MacKay 2014). There was also no association found between general quality of life and health status scores and supplement use.

#### **7.1.18 Reasons for taking**

Some respondents reported taking supplements to rectify a perceived deficiency in their diet or to ameliorate/ as a remedy against their unhealthy diet. This finding was mirrored in another study who found that it was either the health conscious who were taking the supplements or those who were countering a perceived deficiency in their diet (van der Horst and Siegrist 2011).

#### **7.1.19 Financial burden**

This study also set out to establish the estimated monthly cost of the supplements being taken for shoulder pain. The monthly cost ranged from an estimated 30 pence to £48.00, with a median value of £5.50. This financial burden associated with purchasing supplements was reported by some participants, who were not taking supplements, as one of the reasons for not taking them. Taking cod liver oil for shoulder pain was associated with much lower costs than the other supplements and this reflects the retail price of cod liver oil which is 7 pence per one a day in capsule form as compared to 14 pence per one a day in capsule form for high strength omega-3 PUFA (<http://www.seven-seas.com/>).

#### **7.1.20 Limitations**

This study only gives an overview of the likely reasons for consuming dietary supplements for shoulder pain. There was little information collected on the social and psychological factors that might influence supplement use.

The paper based nature of the survey might have been a little cumbersome and better return rates might have been found with an on-line survey. However this paper based method was selected due to the lack of on-line availability at the different sites.

The very nature of the study using a self-reported questionnaire challenges the validity of the information gathered. Self-reported behaviour does not always mirror actual behaviour and the information being collected was personal and possibly controversial, the taking of dietary supplements to promote health or as a self-prescribed treatment (Chandon, Morwitz et al.

2005, Owens, Toone et al. 2014). This effect was minimised by the anonymous nature of the survey.

There was no sample size calculation conducted for this study rather a sample of convenience which carries the inherent bias that the sample is unlikely to be representative of the wider population thereby limiting the ability to make generalisations from the sample here to the wider shoulder pain population. A sample of convenience was chosen in this study due to the restrictions of time and cost on the study. A retrospective sample size calculation with 95% confidence interval and 6% margin of error would suggest that 267 responses were required based on a UK shoulder pain population of 2% of the national population .(Linsell, Dawson et al. 2006).

The design of the questions failed to elicit from the participants if the supplement had been started pre or post the onset of the shoulder pathology. This was not detected in the pilot of the questionnaire but it is highlighted as something which would be important to investigate in any future work.

No association was found between supplement use in the private sector as compared to the NHS. However just under 25% of the returned questionnaires were from the private sector. Therefore, whilst no association was found in the current survey, a more balanced study may identify different findings. The reasons for the fewer responses from the private clinics were a reported lower shoulder caseload than in the larger NHS hospitals. In addition, there were only three private clinics included in the survey, compared to five NHS sites. Future research would benefit from a more balanced recruitment from these two healthcare sectors.

## **Conclusions**

The reasons for taking or not taking dietary supplements for shoulder pain are likely to be numerous and complex and include; social, psychological, economic and educational factors. This study offers an insight into some of the reasons that individuals with shoulder pain take dietary supplements. It has informed the knowledge base of the extent of supplement use in those with shoulder pain and some of the socio demographic drivers for their use.

The mean weekly dose found in this study of EPA and DHA via omega 3 PUFA supplements (1.26g EPA and 0.84g DHA) or cod liver oil (0.40g of EPA and 0.3g DHA) would be considered a

sub-therapeutic dose. With this in mind and the fact that supplement takers generally had adequate intakes of vitamins and minerals from their diet (Public Health England 2014) raises the question; Are supplements being taken for shoulder pain which are unnecessary and a financial burden to the user? However what is unknown is the potential role of dietary supplements in prevention and treatment of shoulder pain or tendinopathy.

The following chapter aims to provide more information on the potential role of dietary supplements in the treatment of RC tendinopathy; a double blind placebo controlled randomised controlled trial investigating the efficacy of long-chain omega-3 PUFAs and exercise in the treatment of RC tendinopathy.

**Chapter 8 : A randomised controlled  
trial of long-chain omega-3  
polyunsaturated fatty acids in the  
treatment of rotator cuff  
tendinopathy**

### **Author's contribution to this chapter**

Fiona Sandford designed the study prepared and sought ethical approval, recruited and assessed subjects from December 2008 – August 2009. Hannah Dollings (research assistant) recruited and assessed participants between August 2009- April 2011 due to two consecutive maternity leave periods for Fiona Sandford. Rashida Pickford and Sarah Friel (research assistants) conducted follow up assessments between May and July 2011. Fiona Sandford continued with the data collection and recruitment from July 2011 until the end of the study. Fiona Sandford prepared the blood samples for analysis and Robert Gray ran the samples through the Gas Chromatograph.

Fiona Sandford inputted all food diary data and analysed the findings.

Fiona Sandford conducted all statistical analyses for this study and has prepared the findings for journal submission.

## Introduction

Evidence suggests that people living in the United Kingdom (UK) consume a diet which is rich in omega 6 polyunsaturated fatty acids (PUFAs) and comparatively low in long-chain omega 3 PUFAs (Public Health England 2014). This is in part due to the fact that the average intake of oily fish, the primary source of dietary long-chain omega-3 PUFA, is well below that of the UK governments recommendation of one oily fish portion per week (NHS). PUFA supplements have been suggested as a means of bridging this deficit. Supplementation with long-chain omega-3 PUFAs as a self-administered intervention has been recommended for a number of health conditions including, heart disease (Kris-Etherton, Harris et al. 2002), asthma (Mickleborough, Lindley et al. 2006), and rheumatoid arthritis (James, Proudman et al. 2010) due to their anti-inflammatory effects.

Rotator cuff (RC) tendinopathy has been associated with inflammation (Longo, Berton et al. 2011), increases in matrix metalloproteinases (Voloshin, Gelinas et al. 2005) and inflammatory cytokines (Gotoh, Hamada et al. 1997, Sakai, Fujita et al. 2001, Blaine, Kim et al. 2005, Voloshin, Gelinas et al. 2005, Molloy, Kemp et al. 2006, Ko, Wang et al. 2008, Millar, Wei et al. 2009, Blaine, Cote et al. 2011, Savitskaya, Izaguirre et al. 2011, Millar, Gilchrist et al. 2015) resulting in the clinical presentation of pain and loss of shoulder function. Although exercise is the main intervention for RC tendinopathy, complete relief of symptoms and restoration of full function is not achieved in all those with this condition (Littlewood, Malliaras et al. 2015). As the outcomes of current surgical and non-surgical treatments are frequently sub-optimal there is the need to explore additional treatment options that may contribute to enhanced outcomes. Supplements of long-chain omega-3 PUFAs have anti-inflammatory effects (James, Proudman et al. 2010) and may be a potential treatment for individuals suffering pain associated with RC tendinopathy (Mavrogenis, Johannessen et al. 2004). The study conducted by Mavrogenis et al (2004) provided a valuable insight in the potential of long-chain omega-3 PUFA and antioxidants in the management of tendinopathy. However, the study was at high risk of bias due to data analysis not being on an intention to treat basis, and the final outcome time point was 32 days, which did not allow for the long term benefit of supplementation to be assessed. It was decided; therefore, to conduct a placebo controlled randomized controlled trial of a long-chain omega-3 PUFA supplement in conjunction with exercise in the treatment of RC tendinopathy.



## Methods

### 8.1.1 Hypotheses

#### *Primary hypothesis:*

Long-chain omega 3 PUFA supplementation will result in significant improvement in disability (as measured by the Oxford Shoulder Score (OSS)) when compared to placebo when assessed at two months, three months, six months and one year.

#### *Secondary hypothesis:*

Long-chain omega 3 PUFA supplementation will result in significant improvement in the experience of pain (as measured by numerical rating score and SF 36) when compared to placebo when assessed at two months, three months, six months and one year.

### 8.1.2 Objectives

To measure disability and function in participants enrolled into a randomised controlled trial of an intake equivalent to 2.6g/day of Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) for two months in men and women with RC tendinopathy.

### 8.1.3 Outcome measures

#### **Primary outcome:**

Disability as measured by OSS.

#### **Secondary Outcomes:**

1. Disability as measured by the Shoulder Pain and Disability Index (SPADI).
2. Pain measured by Numerical Rating Scale (NRS) and Short Form (SF) 36 bodily pain (BP) domain.
3. Quality of life measured by SF 36 and Euro Qol 5D 3L
4. Function measured by Patient Specific Functional Score (PSFS).
5. Global perception of change score.
6. Impairment measures; range of motion and strength.

Full details and justification of the methods used are discussed in chapter 5.

#### **8.1.4 Markers of adherence to the intervention**

Plasma fatty acids, capsules returned and self-report numbers of capsules taken were used as measures of adherence with the supplement intervention. Attendance at the exercise class and documentation of home exercises undertaken gave an indication regarding adherence with exercise intervention.

#### **8.1.5 Study design**

A two arm parallel design randomised placebo-controlled trial with participants randomly allocated to treatment groups. Group allocation was concealed until the study was completed and data for the primary and secondary outcomes had been entered into the statistical database and analysed.

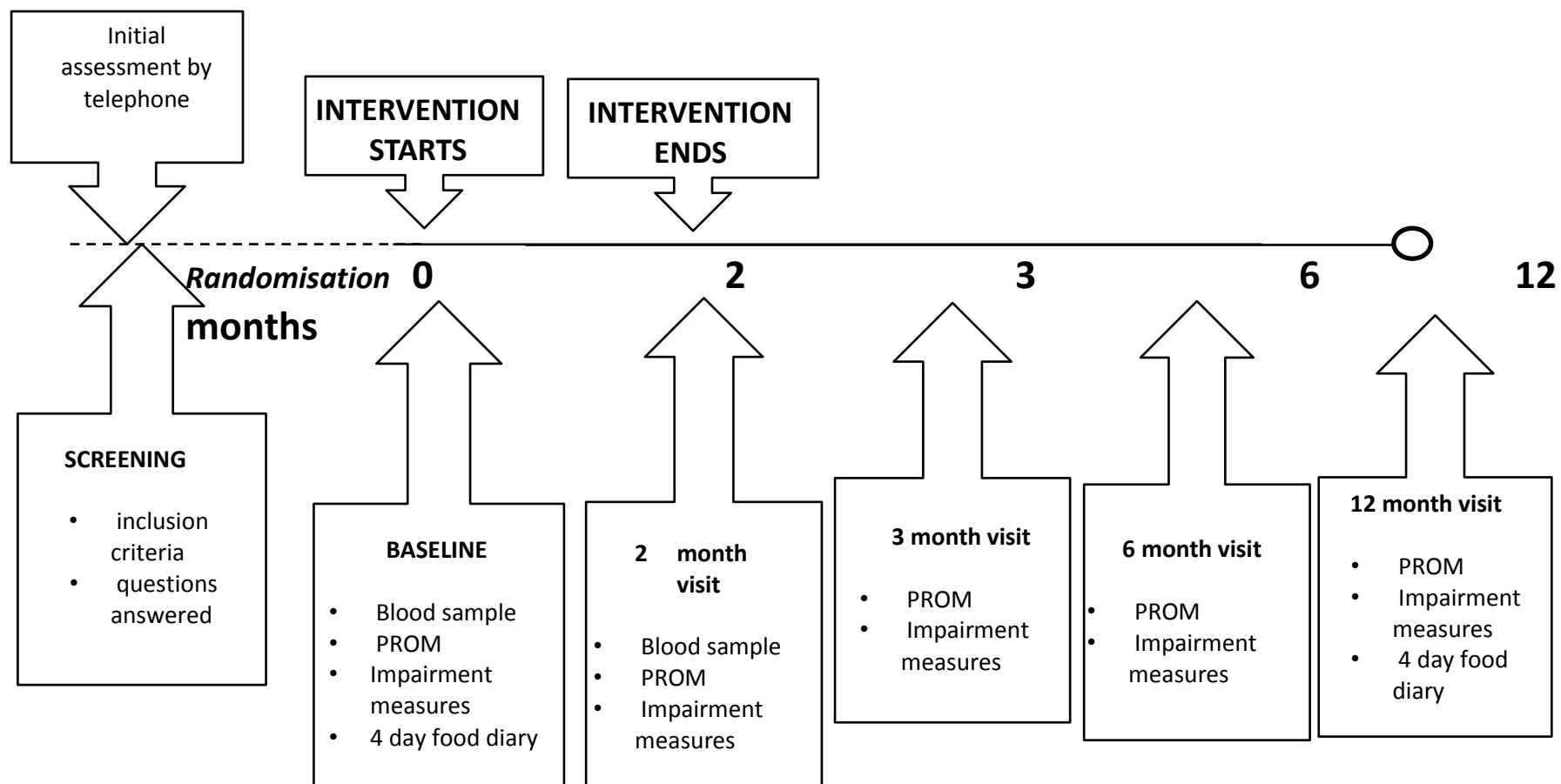


Figure 8.1 Study design

PROM= patient rated outcome measures (OSS, SPADI, NRS, SF36, PSFS, EQD5 and global perception of change).

### **8.1.6 Sample Size**

Sample size calculations were based on a change in OSS as the primary outcome. At the time of the study design and ethics application, the minimal clinically important difference was not published for the OSS, but from previous work (Ainsworth, 2006) was estimated, conservatively, to be 5 which is equivalent to a 21% change from the midpoint of the scale which runs from 0 to 48. A change of 6 has recently been shown to be the minimal important difference (MID) and smallest detectable change (SDC) for the OSS (van Kampen, Willems et al. 2013). The standard deviation of the OSS is based on previous research conducted by Ainsworth (2006) and is 5.87. The sample size was calculated to be 29 subjects in each of the two groups (58 in total), to detect a 5 point change at  $P < 0.05$  with a 90% power. Allowing for a dropout rate of 10% (Ainsworth, Lewis et al. 2009), the study aimed to randomise 32 participants into each arm of the investigation.

### **8.1.7 Test materials**

The active treatment used in this trial MaxEPA (Seven Seas Ltd, Hull, UK, MHRA product licence 19488/0353). These capsules were provided as opaque gelatine coated capsules, oval in shape and brown tan in colour to disguise the content, containing 170mg EPA, 115mg DHA, 2 units/g tocopherols acetate (vitamin E). The placebo supplement looked identical and contained a mixed inert oil (olive oil BP containing the same amount of vitamin E and antioxidants as the active treatment) and did not contain any EPA or DHA with the EPA and DHA being replaced by oleic acid. Participants in both groups were asked to take nine soft shell capsules per day for a total of two months. The capsules were supplied in identical plain white plastics tubs which had a tamper proof seal. Each participant was supplied with three tubs of capsules containing 201 capsules per tub, 603 in total. The participants were requested to return any unused capsules at the end of the study.

The instructions of how and when to take the capsules were stuck on the tubs of supplements and reiterated to the participants verbally.

#### **8.1.7.1 Recruitment of participants**

The study aimed to recruit men and women aged 18 to 80 years, who were referred to physiotherapy for treatment at one of four participating NHS physiotherapy departments within London, UK.

Inclusion criteria were:

- (i) Unilateral shoulder pain of more than 3 months duration.
- (ii) Pain produced or increased during shoulder flexion and/or abduction and/or external rotation of the symptomatic shoulder.
- (iii) At least four of the following: positive Neer's impingement sign, positive Hawkins & Kennedy test, pain and weakness reproduced on full and/or empty can test, pain and weakness on resisted shoulder external rotation, pain on palpation over greater tuberosity of the humerus.

Exclusion criteria were:

- (i) Allergy to or unwilling to take fish oils, current use (over 1g/d) fish oils.
- (ii) Diabetes.
- (iii) Pregnancy or breast feeding.
- (iv) Reproduction of shoulder symptoms during active cervical spine movements.
- (v) Post traumatic onset of symptoms.
- (vi) Radiographic or clinical evidence of shoulder instability (sulcus, anterior/posterior draw, relocation test, apprehension test).

Participants were recruited once they had been referred to physiotherapy from their treating physiotherapist at the initial assessment session, who provided the individual with the patient information leaflet (Appendix 11.14) and if the potential participant expressed interest in taking part in the study, consent was sought for the chief investigator (CI) to telephone or email the individual. During the subsequent telephone conversation the screening questions were reassessed, and the study protocol described to the potential participant. If the potential participant provided verbal consent to take part in the research an appointment was arranged within the Guy's and ST Thomas' Trust Clinical Research facility located at St Thomas' Hospital, London SE1, to perform screening tests, obtain written consent and to conduct the baseline assessment.

#### **8.1.8 Ethical approval, clinical governance and R&D approval**

Ethical approval was obtained from Bromley Research Ethics Committee, Bromley Primary Care Trust, Bassetts House, Broadwater Gardens, Farnborough, Kent BR6 7UA (REC ref: 08/H0805/21) on 28<sup>th</sup> May 2008 (Appendix 11.13). Participants gave written informed consent (Appendix 11.15) and received remuneration for public transport travel costs involved in taking part in the study.

This trial was registered at Current Controlled Trials (<http://www.controlled-trials.com> as ISRCTN17856844).

#### **8.1.9 Data analysis**

Statistical analysis of the data was conducted using SPSS for windows version 22.0 (IBM Software, Hampshire, UK). Standard distributional checks were made, and where appropriate, analyses were attempted following log transformation.

The data was analysed on an intention-to-treat basis, including all randomised participants whom provided follow up data and each participant was analysed in their original randomized groups. Treatment effects are shown as the comparisons between the treatment groups at each outcome point during of the study, adjusted for baseline values.

Analysis of covariance (ANCOVA) tests were carried out for a within subject factor (assessment time point) and a between group factor (supplement type; placebo or treatment) with OSS as the dependent variable, the treatment allocation as the predictor factor, age, gender and body mass index (BMI) as co-variates and the baseline OSS as an offset variable. A mixed model ANCOVA analysis was also used to look for change over the whole study period in each outcome measure adjusting for the baseline measurements. Similar analyses were conducted for secondary outcomes efficacy analysis; ANCOVA and mixed model ANCOVA.

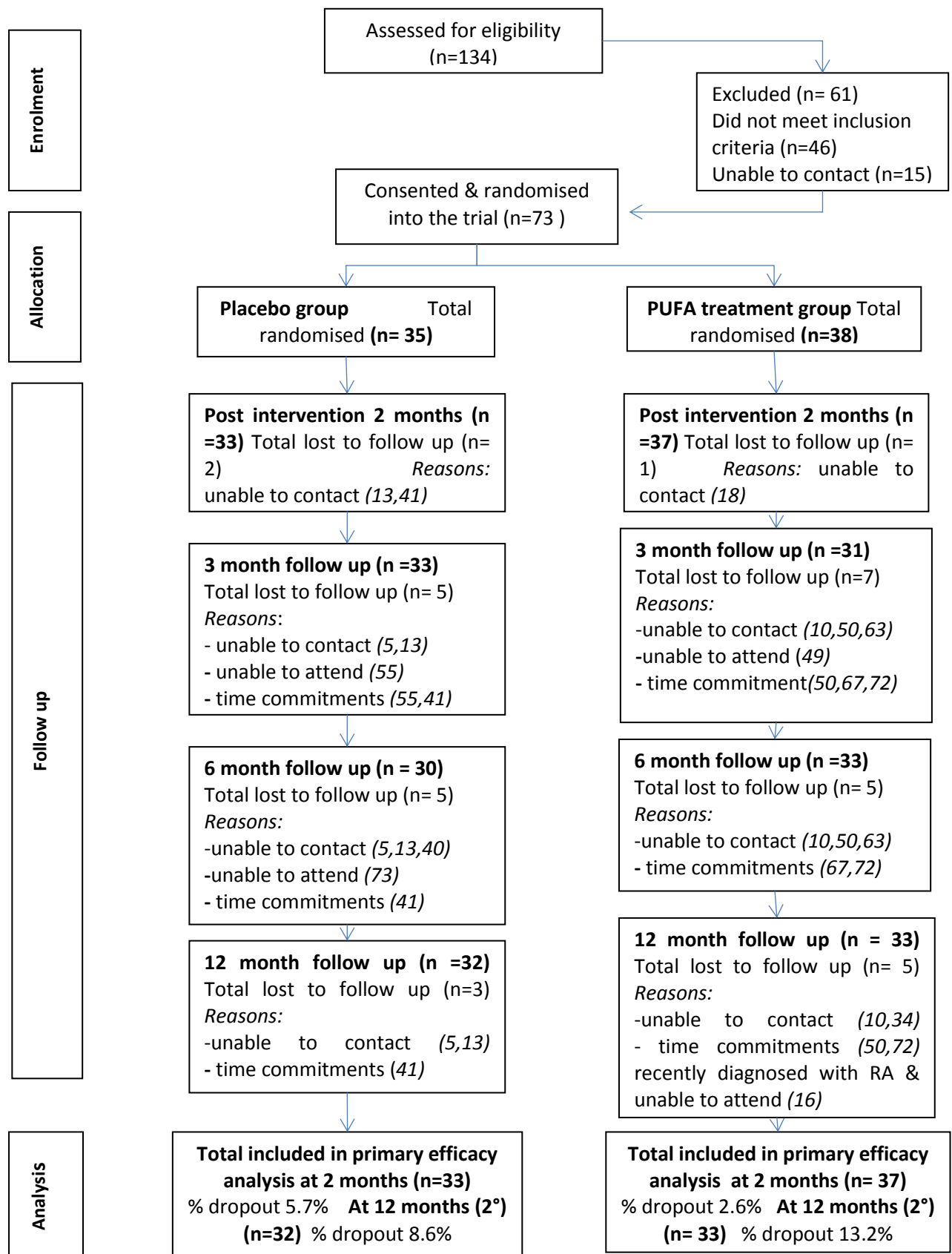
## **Results**

#### **8.1.10 Participant recruitment**

During the recruitment period of December 2008 to January 2013, 134 patients were identified, by physiotherapists at the four participating sites for inclusion into the study. Following either a telephone conversation or a face to face meeting with the chief investigator (CI) or principal investigator (PI), 61 of these potential participants were deemed ineligible or they declined to be recruited into the trial.

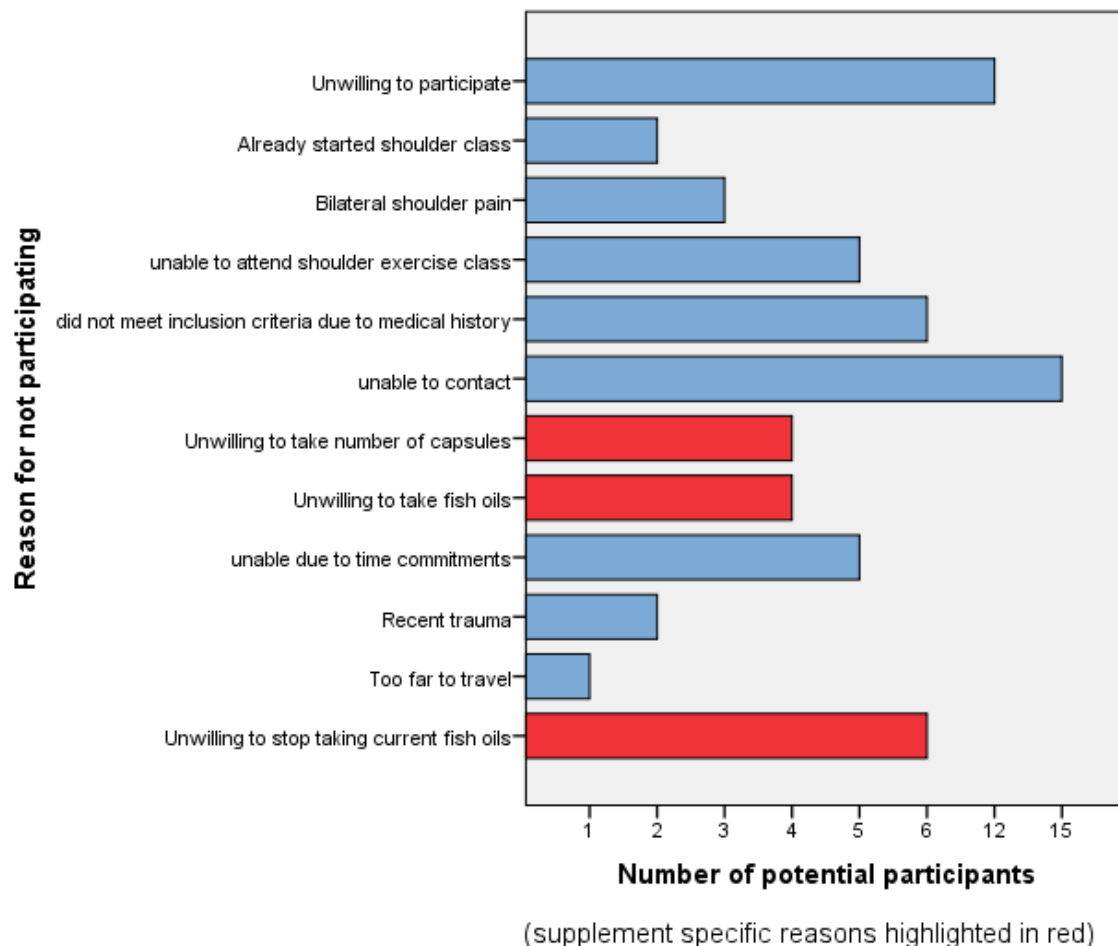
The reasons for the exclusion of potential participants deemed ineligible or who declined to be consented into the trial are detailed in Figure 8.3. In total 73 participants were consented into the study.

Figure 8.2 CONSORT diagram



Fourteen potential participants declined to take part due to either having to start taking or change their current fish oil use. The red bars in Figure 8.3 detail their reasons.

Figure 8.3 Reasons for exclusion of potential participants



#### 8.1.11 Participant retention and attrition

At two months 71 (96%) participants were reassessed; at three months 62 (85%) participants were reassessed; at six months 63 (86%) participants were reassessed; and at twelve months 65 (89%) participants were reassessed. There was no statistically significant difference in the attrition rate between groups. Participant attrition and retention during the study are presented in a CONSORT diagram (Figure 8.2).



#### **8.1.12 Participant demographic characteristics**

The baseline participant demographics in each treatment group and the baseline outcome measures are presented in Table 8.1 and Table Appendix 11.21) respectively. More participants in the placebo group reported use of analgesic medication ( $P=0.02$ ; Chi-squared test) but otherwise there were no other significant differences between groups.

Table 8.1 Participant demographic data

Variable	Placebo n=35	Treatment n=38
Gender: male	20 (57.1%)	17 (44.7%)
Age (years)	52.03 (16.19)	52.24 (12.0)
Body mass index (kg/m <sup>-2</sup> )	28.85 (8.44)	27.45 (5.17)
Waist circumference (cm)	98.84 (16.41)	94.81 (12.97)
Current smoker	5 (14.3%)	5 (14.3%)
Plasma EPA & DHA (wt%)	3.85 (1.48)	4.07 (1.82)
Analgesia medication	10 (28.6%)*	3 (7.9%)
Statin medication	7 (20%)	6 (15.79%)
Symptom duration (months)	10 (4-18)	9 (6-19.5)
<i>Mechanism of injury:</i>		
Insidious	17 (48.6%)	21 (55%)
Accident/fall	5 (14.3%)	8 (21.1%)
Lifting/repetitive movement	6 (17.1%)	6 (15.8%)
Exercise	7 (20.0%)	3 (7.9%)
Able to sleep on symptomatic shoulder	17 (48.6%)	17 (44.7%)
<i>Aggravating movement:</i>		
Flexion	23 (65.7%)	20 (52.6%)
Abduction	4 (11.4%)	5 (13.2%)
Hand behind back	4 (11.4%)	10 (26.3%)
External rotation	1 (2.9%)	0 (0%)
None	3 (8.6%)	3 (7.9%)

Legend: n=number, EPA= eicosapentaenoic acid, DHA=docosahexaenoic acid, wt%= percentage weight. Summary measures represent means/N (SD/ %/range). Differences between groups test with Mann-Whitney test or Chi-squared test. \* denotes P=0.03

### 8.1.13 Baseline characteristics of participants completing and those not completing the trial

Although not necessary due to the very low rate of missing data, a post hoc analysis has been performed to explore the data to establish whether there were any significant differences between those who completed the trial to the primary outcome point (two months) and the one year point and those who did not.

There were no statistical differences between the baseline characteristics population who completed the intervention and attended for assessment at the primary end point (two months) and those who did not. Further details can be found in Appendix 11.22.

### 8.1.14 Adherence to the interventions

There was no significant difference between groups in the number of capsules taken throughout the intervention from either the returned capsules count (mean difference= 38.17 during the two months, 95%CI of the difference= 102.69; 26.04, p=0.24 analysed using independent t test) or the documented capsules consumption (mean difference= 16.87 capsules during the two months, 95%CI of the difference= -92.82 to 59.07; p=0.66 analysed using independent t test). This information is detailed in Table 8.2.

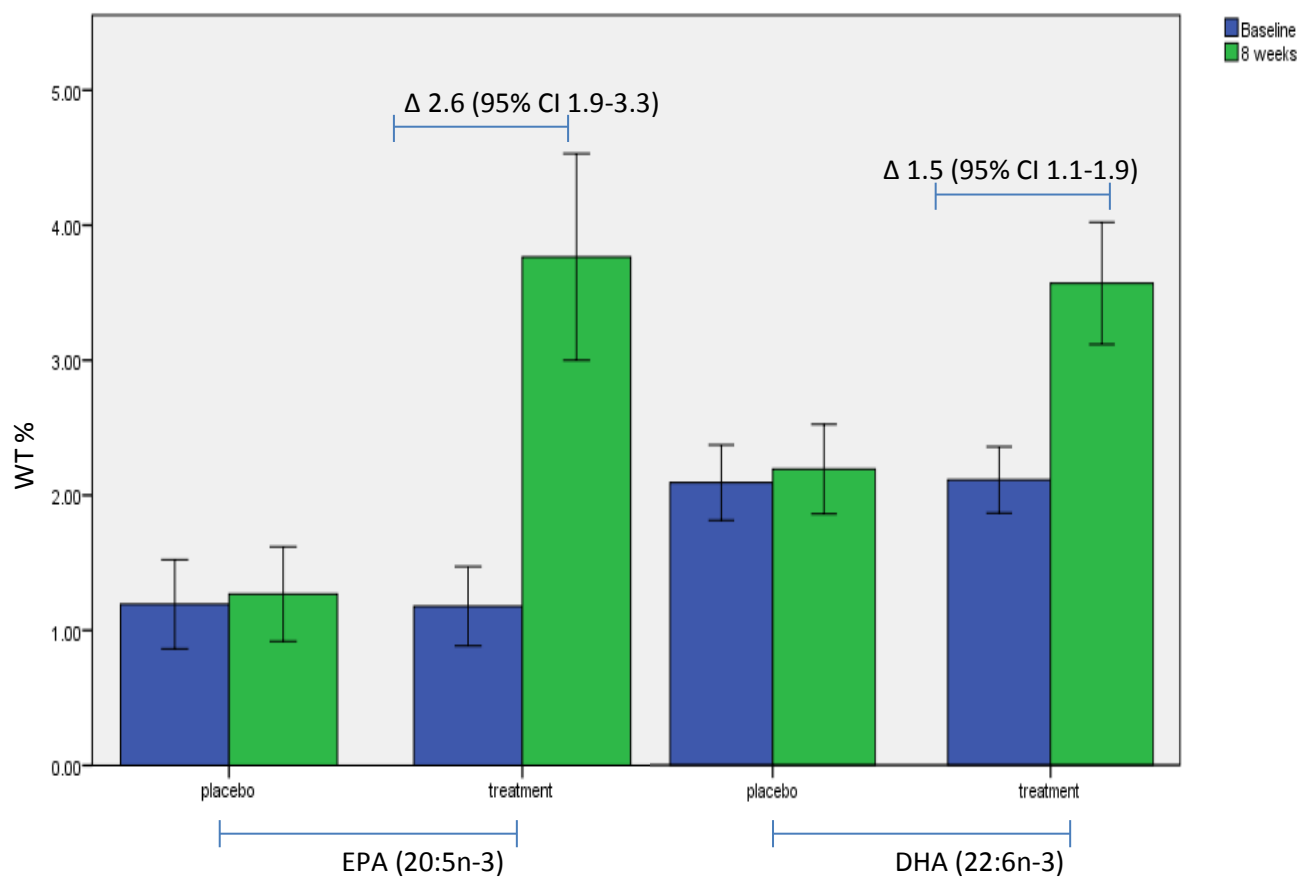
Table 8.2 Showing the number of capsules taken according to the pill count and documented in the diaries

	Placebo	Treatment	P Value
Number of capsules taken from count	n=27 425 (122)	n=34 463 (126)	0.24
% of capsules taken	84% (24%)	92% (25%)	
Documented capsules taken in diary	n= 21 406 (133)	n= 26 423 (125)	0.66
%of capsules taken	81% (26%)	84% (25%)	

Legend; n= number. Summary measures are means and (SD) analysed using independent samples t test.

There was a statistically significant difference in the blood plasma levels of long-chain omega-3 PUFAs (EPA and DHA) at the end of the intervention between the two groups (mean difference=2.35, 95%CI= 1.58,3.12,  $p<0.001$ ). This information is detailed in Figure 8.4.

Figure 8.4 Graph showing the rise in EPA and DHA plasma levels within the treatment group, within group comparisons made using a paired samples t test.



Legend: EPA= eicosapentaenoic acid, DHA= docosahexaenoic acid, wt%= percentage weight, Δ= mean difference and 95% confidence interval between baseline and follow-up.

Table 8.3 Details the plasma fatty acid analysis pre and post intervention in the treatment and placebo groups.

Fatty Acid	Baseline (n=73)	Placebo (n=33)	Treatment (n=36)	Treatment effect	P value
SFA	28.19 (4.04)	28.77 (2.59)	27.77 (3.40)	-1.06 (-4.26, 2.14)	0.51
14:0	1.22 (0.38)	1.14 (0.45)	1.14 (0.33)	0.05 (-0.13, 0.22)	0.58
16:0	20.28 (2.01)	20.52 (1.49)	19.57 (2.19)	-0.71 (-1.42, -0.01)	0.05
18:0	7.08 (1.12)	7.11 (0.65)	7.06 (0.88)	0.07 (-0.16, 0.29)	0.09
MUFA	22.28 (5.35)	22.98 (3.95)	20.55 (4.92)	-1.50 (-4.29, 1.30)	0.29
16:1 $n$ -7	1.70 (0.62)	1.58 (0.53)	1.60 (0.56)	0.07 (-0.14, 0.28)	0.49
18:1 $n$ -9	19.43 (4.38)	19.98 (3.24)	17.47 (4.14)	-1.76 (-3.09, -0.43)	0.01
18:1 $n$ -7	1.45 (0.20)	1.42 (0.18)	1.48 (0.22)	0.10 (0.03, 0.17)	0.01
PUFA	38.39 (6.15)	39.92 (9.76)	41.58 (10.05)	1.09 (-3.70, 5.88)	0.65
18:2 $n$ -6	25.23 (3.97)	26.28 (5.21)	24.54 (3.70)	-1.69 (-3.03, -0.34)	0.02
20:3 $n$ -6	1.61 (0.85)	1.45 (0.28)	1.17 (0.32)	-0.29 (-0.44, -0.14)	<0.01
20:4 $n$ -6	6.42 (1.83)	6.36 (1.56)	6.02 (1.45)	-0.44 (-0.91, 0.03)	0.07

Fatty Acid	Baseline (n=73)	Placebo (n=33)	Treatment (n=36)	Treatment - placebo (95%CI)	P value
22:4n-6	0.34 (0.13)	0.36 (0.11)	0.32 (0.12)	-0.01 (-0.05, 0.03)	0.62
22:5n-6	0.49 (0.21)	0.57 (0.16)	0.55 (0.16)	0.02 (-0.03, 0.08)	0.43
18:3n-3	0.87 (0.31)	0.81 (0.26)	0.89 (0.32)	0.07 (-0.04, 0.18)	0.19
20:5n-3	1.21 (0.90)	1.27 (0.99)	3.67 (2.27)	2.35 (1.58, 3.13)	<0.001
22:5n-3	0.60 (0.17)	0.63 (0.25)	0.90 (0.38)	0.28 (0.16, 0.40)	<0.001
22:6n-3	2.14 (0.78)	2.19 (0.94)	3.52 (1.33)	1.28 (0.83, 1.74)	<0.001

Mean values (SD) and treatment effect is active treatment – placebo (95% CI). Probability is derived from ANCOVA with the treatment value as the dependent variable and the treatment group as the between subject factor with baseline value, age, gender and BMI as covariates. SFA= saturated fatty acid, MUFA= monounsaturated fatty acid, PUFA= polyunsaturated fatty acid.

The number of shoulder classes attended did not differ between groups (treatment-placebo mean difference=-1.14 classes, 95%CI of the difference= -0.05, 2.79; p= 0.10). The mean attendance in the placebo group as ranked by the criteria set out in the method (Chapter 5) was classed as good (attended six to seven classes out of the eight available, mean= 6.58 classes, SD= 2.06) and the mean attendance in the treatment group was satisfactory (attended four to five classes out of the eight available, mean= 5.20 classes, SD=2.89).

There were no differences in reported home exercise duration: those in the placebo group documented a mean of 11.74 (SD=9.80) minutes per day and the treatment group 10.74 (SD= 7.27) minutes per day.

### **8.1.15 FUNCTION**

#### **8.1.15.1 Primary outcome: Oxford Shoulder Score (OSS)**

##### **8.1.15.1.1 Primary efficacy analysis- intention to treat analysis**

Both groups demonstrated a significant reduction in disability, as measured by the OSS, at each follow-up when compared to the baseline. There was on average a 25% reduction in disability (95% CI =15.34, 34.62) in the placebo group and 25% reduction (95% CI=13.48, 36.23) in the intervention group at two months from baseline (Table 8.5). The mean improvement in the OSS score at two months was 8.22 in the placebo group and 6.65 in the treatment group. Both of these represent a clinically meaningful change in disability (van Kampen, Willems et al. 2013).

There was no statistically significant difference in the change in the primary outcome, OSS score, between the two groups at two months (adjusted mean difference= -0.07, 95%CI (-2.61, 2.46) P=0.95) and up to 12 months (adjusted mean difference= -0.34, 95%CI (-3.29, 2.60) P=0.82). These results are displayed in Table 8.4 and Figure 8.5.

The differences for the improvement in the OSS scores between groups using a mixed model analysis up to 12 months indicated no significant treatment effect (P=0.89,(95%CI=-1.29,1.84).

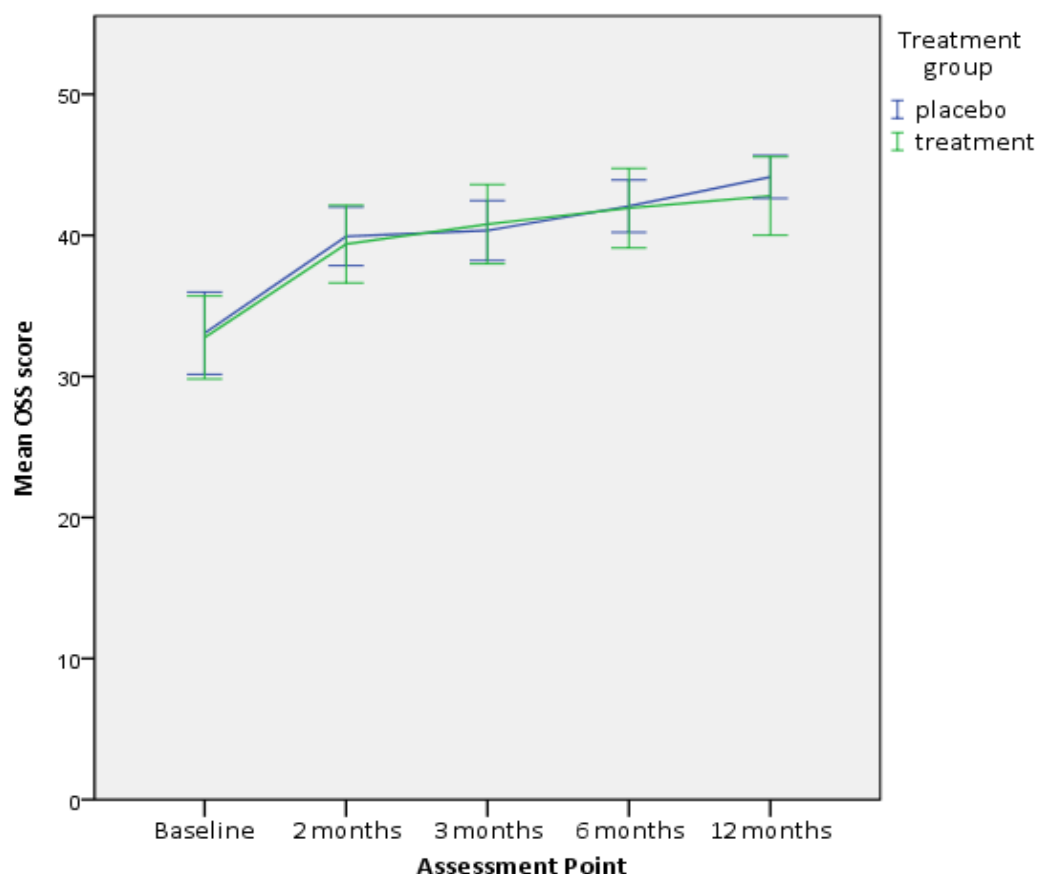
Table 8.4 Oxford Shoulder Score (OSS) at each assessment point

Time point	Placebo	Treatment	Treatment Effect (95% CI)	P t-test	P Ancova
Baseline	n=35, 31.71(8.40)	n=38, 32.03(7.85)			
2 months	n=33, 39.93 (7.2) $\Delta=25\%$ (15-34)	n=37, 38.68 (8.02) $\Delta=25\%$ (14-36)	-0.23 (-3.89,3.43)	0.95	0.82
3 months	n=31,39.45 (6.62) $\Delta=27\%$ (16-37)	n=31, 40.48 (7.4) $\Delta=30\%$ (17-42)	-0.57 (-2.54, 4.60)	0.56	0.3
6 months	N=30, 42.10(4.81) $\Delta=33\%$ (21-46)	N=33, 41.61(7.18) $\Delta=35\%$ (20-51)	-0.49 (-3.60, 2.62)	0.73	0.91
12 months	N=32, 43.06(5.50) $\Delta=41\%$ (27-55)	N=33, 43.03(6.93) $\Delta=38\%$ (22-55)	-0.03 (-3.14, 3.07)	0.82	0.89

Legend; n= number, CI= 95% confidence interval of the difference. Summary measures are means and (SD) analysed using independent samples t test and between group comparison by ANCOVA adjusted for baseline value, age, gender and BMI.  $\Delta$ = percentage change from baseline (95% CI of change). Treatment effect is the difference between active treatment and placebo.



Figure 8.5 Oxford Shoulder Score (OSS) at each assessment point. Error bars= 95% confidence interval



#### 8.1.15.1.2 Participants achieving clinically important change in disability

The primary outcome time point was eight weeks, and at this time-point 16/37 (43.2%) of the participants in the PUFA supplement group and 15/33 (45.4%) of the participants in the placebo group demonstrated a clinically important improvement in perceived level of disability (a six point or higher improvement on the OSS). No participants in the placebo group and 1/37 (2.7%) in the treatment group showed a clinically important deterioration (a six point or higher reduction in OSS) at this time point. There was no statistically significant difference between the supplement groups for the clinically important improvement ( $p=0.85$ ) and clinically important deterioration ( $p=0.34$ ).

At three months, 22/31 (71%) of the PUFA supplement group and 20/31 (64.5%) of the placebo group reported a clinically important improvement in perceived level of disability

( $p=0.58$ ). No participants in either group reported a clinically important deterioration in perceived level of disability.

At six months 21/33 (63.6%) of the participants in the PUFA supplement group and 20/30 (66.7%) of the participants in the placebo group demonstrated a clinically important improvement in perceived level of disability (a six point or higher improvement on the OSS). No participants in the placebo group and 2/33 (6.1%) in the treatment group showed a clinically important deterioration (a six point or higher reduction in OSS) at this time point. There was no statistically significant difference between the supplement groups for the clinically important improvement ( $p=0.80$ ) and clinically important deterioration ( $p=0.17$ ).

At the final assessment point, one year, 26/33 (78.8%) of the participants in the PUFA supplement group and 23/32 (71.9%) of the participants in the placebo group demonstrated a clinically important improvement in perceived level of disability (a six point or higher improvement on the OSS). No participants in the placebo group and 1/33 (3%) in the treatment group showed a clinically important deterioration (a six point or higher reduction in OSS) at this time point. This participant reported re-injuring their shoulder whilst lifting a heavy object between three and six months and self-referred to her general practitioner.

There was no statistically significant difference between the two groups for the clinically important improvement ( $p=0.52$ ) and clinically important deterioration ( $p=0.32$ ).

#### **8.1.15.2 Secondary outcomes: Shoulder Pain and Disability Index (SPADI)**

A statistically significant reduction in level of perceived disability as measured by SPADI was observed in both groups over the duration of the study (two months; placebo mean difference= 16.93, 95% CI=10.93, 22.93,  $p=0.00$ , long-chain omega-3 PUFA mean difference= 15.85, 95%CI= 9.52, 22.17,  $p=0.00$ ; 12 months; placebo mean difference= 15.73 95%CI= 8.15, 23.30,  $p=0.00$ , long-chain omega-3 PUFA mean difference= 7.82, 95%CI=0.93, 14.71,  $p=0.03$ ).

The PUFA supplement group showed a statistically significant change when compared to the placebo group (adjusted mean difference= -8.25, 95%CI=-15.56, -0.94;  $p=0.03$ , analysed by ANCOVA adjusted for baseline) at three months (Table 8.5 and Figure 8.6). It would be questionable whether a difference of 8.25 is clinically meaningful when the MICD of the SPADI

has been reported to range from 8-20 (Williams, Holleman et al. 1995, Paul, Lewis et al. 2004, Schmitt and Di Fabio 2004, Ekeberg, Bautz-Holter et al. 2010). The line graph shows clearly that the mean SPADI score then remained almost static at that level in the long-chain omega-3 PUFA supplement group from three months to the end of the trial at 12 months. This suggests that the treatment group reached almost maximal improvement at three months which was nine months earlier than the placebo group who had a higher mean SPADI (greater disability) score at three months and continued to improve more slowly to the six month outcome point and end of the trial at 12 months.

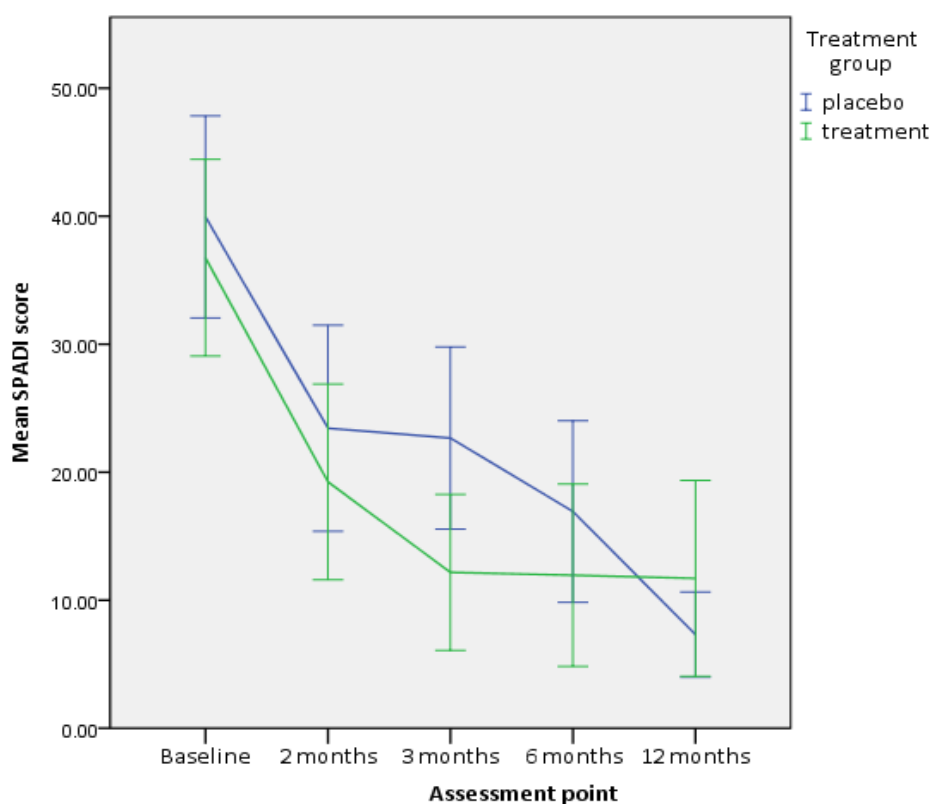
There were no significant differences reported for the reduction in the SPADI scores between groups using a mixed model analysis up to 12 months (p=0.38).

Table 8.5 Shoulder pain and disability index (SPADI) scores across all assessment points

Time point	Placebo	Treatment	Treatment effect (95% CI)	P value
Baseline	n=35, 43.12 (21.49)	n=38, 38.74 (22.27)		
2 months	n=33, 25.10 (22.78)	n=36, 23.43 (23.07)	0.27 (-8.26, 8.80)	0.95
3 months	n=31, 25.34 (21.09)	n=31, 13.89 (18.14)	-8.49 (-16.24 -0.73)	0.03
6 months	n=30, 16.85 (18.33)	n=33, 13.26(19.01)	-3.00 (-12.10, 6.11)	0.51
12 months	n= 32, 9.85 (2.39)	n= 33, 11.20(19.2)	2.03 (-6.38, 10.49)	0.63

Legend: n=number CI=95%confidence interval of the difference. Summary measures are mean values with SD in parenthesis. Probability is from an independent samples t test and between group treatment effects are derived from univariate ANCOVA adjusted for baseline value, age, gender and BMI. Treatment effect is the difference between active treatment and placebo.

Figure 8.6 Shoulder pain and disability index (SPADI) score across all assessment points. Error bars= 95% confidence interval.



#### 8.1.15.3 Patient Specific Functional Score (PSFS)

A statistically significant improvement in function, as measured by the Patient Specific Functional Score (PSFS), was demonstrated by participants in both groups throughout the duration of the study (two months; placebo mean difference= -21.16, 95% CI= -34.42, -10.90,  $p=0.00$ , long-chain omega-3 PUFA mean difference= -28.24, 95% CI= -38.04, -18.45,  $p=0.00$ ; 12 months; placebo mean difference= -19.69 95% CI= -29.97, -9.41,  $p=0.00$ , long-chain omega-3 PUFA mean difference= -13.26, 95% CI= -22.74, -3.79  $p=0.00$ ).

There were no between group differences in functional improvement as measured by the PSFS at any time point up to 12 months (adjusted mean difference= 1.55, 95% CI= -9.81, 12.90,  $p=0.79$  using ANCOVA adjusted for baseline).

There were no significant differences found in the PSFS scores between groups using a mixed model analysis up to 12 months ( $p=0.39$ ).

Table 8.6 details the Patient specific functional score across all time points for both groups

Time point	Placebo	Treatment	Treatment effect (95% CI)	P value
Baseline	n=35, 38.38 (19.73)	n=38, 36.75 (20.44)		
2 months	n=33, 58.43 (24.07)	n=37, 64.55 (24.07)	6.08 (-5.96, 18.11)	0.32
3 months	n=31, 68.87 (22.42)	n=31, 72.04 (21.90)	5.19 (-6.12, 16.49)	0.36
6 months	n=30, 72.89 (21.20)	n=33, 76.57 (21.25)	5.18 (-5.67, 16.02)	0.34
12 months	n=32, 78.80 (23.77)	n=33, 80.44 (21.81)	4.17 (-6.68, 16.10)	0.41

Legend: n=numbers, CI=95% confidence interval of the difference. Summary measures are means and (SD) analysed using independent samples t test and treatment effects (difference between active and placebo treatments) are derived from univariate ANCOVA adjusted for baseline value, age, gender and BMI.

### 8.1.16 PAIN

Pain within the study was measured using the Numerical Rating Scale (NRS) and Short form 36 (SF36) bodily pain (BP) component score.

#### 8.1.16.1 Numerical Rating Scale (NRS)

A statistically significant reduction in level of reported pain as measured by NRS was observed in both groups over the duration of the study (at two months; placebo mean difference= 2.18 (95% CI=1.24, 3.12,  $p<0.01$ ), long-chain omega-3 PUFA mean difference= 2.13 (95%CI= 1.10, 3.14,  $p<0.01$ ); at 12 months; placebo mean difference= 1.95 (95%CI= 0.87, 3.04,  $p=0.01$ ), long-chain omega-3 PUFA mean difference= 1.18 (95%CI=0.04, 2.31,  $p=0.04$ ).

There were no statistically significant between group differences in reduction of pain levels at the primary outcome point at two months (adjusted mean difference=0.26 (95%CI= -0.04, 0.56,  $p=0.08$  using ANCOVA adjusted for baseline) and also at 12 months (adjusted mean difference= 0.27 95%CI= -0.03, 0.57  $p=0.07$  using ANCOVA adjusted for baseline).

There were also no significant differences found in the improvement in the NRS scores between groups using a mixed model analysis up to 12 months (p=0.50).

Table 8.7 details the Numerical rating scale scores across all time points for both groups

Time point	Placebo	Treatment	Treatment effect (95%CI) <sup>+</sup>	P value
Baseline	n=35, 6.26 (1.83)	n=38, 6.0 (2.14)		
2 months	n=33, 4.0 (2.47)	n=36, 3.75 (2.51)	-0.07 (-1.28, 1.15)	0.91
3 months	n=31, 3.53 (2.49)	n=31, 2.56 (2.05)	-0.92 (-2.09, 0.26)	0.12
6 months	n=30, 3.30 (2.68)	n=32, 2.86 (2.44)	-0.24 (-1.73, 1.25)	0.75
12 months	n= 32, 2.11 (2.39)	n= 33, 2.1 (2.53)	0.04 (-1.18, 1.26)	0.95

Legend: n=numbers, CI=95% confidence interval of the difference. Mean values (SD). Treatment effect is the difference in change from baseline between groups with 95% CI adjusted for age, gender and BMI. Probability is from analysis of variance at each time point.

#### 8.1.16.2 SF 36 Bodily Pain

Both treatment groups showed a statistically significant decrease in pain as measured by the SF36 (BP) at the primary outcome point of two months (placebo, mean difference= -14.25, 95%CI= -19.29, -9.21, p= 0.00 and long-chain omega-3 PUFA mean difference= -15.11, 95%CI= -22.89, -7.33, p=0.00 using ANCOVA adjusted for baseline). At the longevity outcome point of 12 months only the long-chain omega-3 PUFA supplement group showed a statistically significant change (placebo mean difference= -5.13, 95%CI= -14.95, 4.69, p=0.30 and long-chain omega-3 PUFA mean difference= -9.30, 95%CI= -16.82, -1.78, p=0.02 using ANCOVA adjusted for baseline) demonstrated a reduction in pain as measured by the SF36 (BP) score over the 12 month period.

There was no statistically significant difference between groups at the primary outcome point of two months (mean difference= 1.79, 95%CI= -6.17, 9.75 p=0.66 using ANCOVA adjusted for baseline) or at 12 months (mean difference= 9.37, 95%CI= -1.08, 19.83, p= 0.08 using ANCOVA adjusted for baseline).

Table 8.8 details the SF 36 Bodily Pain scores across all time points for both groups.

<b>Time point</b>	<b>Placebo</b>	<b>Treatment</b>	<b>Treatment effect (95% CI)</b>	<b>P value</b>
<b>Baseline</b>	n=35, 47.89(19.07)	n=38, 51.61(21.70)		
<b>2 months</b>	n=32, 64.66(19.72)	n=36, 67.31(18.09)	1.73 (-6.29, 9.74)	0.67
<b>3 months</b>	n=31, 62.23(20.29)	n=31, 71.06(19.09)	6.69 (-1.79, 15.16)	0.12
<b>6 months</b>	n=30, 73.37(18.25)	n=32, 74.47(21.46)	2.87 (-6.13, 11.86)	0.53
<b>12 months</b>	n= 32, 69.63(22.20)	n= 32, 80.22(19.39)	11.57 (0.85, 22.30)	0.04

Legend: n=numbers, CI=95% confidence interval of the difference. Summary measures are means and (SD) analysed using independent samples t test and treatment effects (difference between active and placebo treatments) are derived from univariate ANCOVA adjusted for baseline value, age, gender and BMI.

### 8.1.17 HEALTH RELATED QUALITY OF LIFE MEASURES

#### 8.1.17.1 EQ 5D-3L

There was no statistically significant improvement found in health related quality of life function, as measured by the EQ 5D 3L, demonstrated by participants in either group throughout the duration of the study, other than for the placebo group at 12 months (two months; placebo mean difference= -0.04, 95% CI=-0.11, 0.04, p=0.33, long-chain omega-3 PUFA mean difference= -0.10, 95%CI= -0.18, -0.03, p=0.10; 12 months; placebo mean difference= -0.08, 95%CI= -0.14, -0.01, p=0.02, long-chain omega-3 PUFA mean difference= -0.02, 95%CI= -0.10, 0.05, p=0.54 using ANCOVA adjusted for baseline).

There were no statistically significant between group differences for change in health related quality of life over the study period (two months; mean difference= 0.58, 95%CI=-0.03, 0.14 p=0.18; 12 months mean difference=0.82, 95%CI= -0.05, 0.10, p=0.45).

There were no significant differences found in the EQ5D 3L score changes between groups using a mixed model analysis up to 12 months (p=0.26).

Table 8.9 details the EQ 5D 3L scores across all time points in both groups.

Time point	Placebo	Treatment	Treatment effect (95% CI)	P value
Baseline	n=34, 0.68 (0.23)	n=38, 0.70 (0.26)		
2 months	n=33, 0.74 (0.17)	n=37, 0.79 (0.23)	0.06 (-0.03, 0.15)	0.17
3 months	n=30, 0.78 (0.13)	n=31, 0.82 (0.16)	0.27 (-0.04, 0.10)	0.44
6 months	n=30 0.80 (0.19)	n=33, 0.83 (0.13)	0.03 (-0.04, 0.10)	0.46
12 months	n= 32, 0.82 (0.15)	n= 33,0.86(0.17)	0.05 (-0.02, 0.12)	0.17

Legend: n=numbers, CI=95% confidence interval of the difference. Summary measures are means and (SD) analysed using independent samples t test and treatment effects (difference between active and placebo treatments) are derived from univariate ANCOVA adjusted for baseline value, age, gender and BMI.

#### 8.1.17.2 EQ D5-3L – health status

The EQ D5 measuring health status showed that only the treatment group showed a statistically significant improvement in health status at the primary outcome point (placebo mean difference= -2.94 95%CI=-8.21, 2.33, p=0.26, long-chain omega-3 PUFA group, mean difference=-10.36, 95%CI= -16.52, -4.20, p=0.00). Neither group showed an improvement in health status in the period two to 12 months (placebo mean difference= -0.13, 95%CI= -8.37, 8.12, p=0.98, omega3 PUFA mean difference= 2.65, 95%CI= -4.99, 10.28, p=0.49).

There were no statistically significant between group differences for change in health status at two months (mean difference= 3.78, 95%CI= -2.07, 9.62, p=0.20 using ANCOVA adjusted for baseline), or 12 months (mean difference= 1.16, 95%CI=-8.25, 10.56, p=0.81).

There were no significant differences found for change in health status between groups using a mixed model analysis up to 12 months (p=0.19). Table 8.11 details the EQ 5D Health Status scores across all time points for both groups.



Table 8.10 EQ 5D Health status scores across all assessment points

Time point	Placebo	Treatment	Treatment effect (95% CI)		P value
Baseline	n=34, 72.91 (13.59)	n=38, 70.24(19.39)			
2 months	n=33, 78.27 (13.94)	n=36, 80.19(12.00)	4.44	(-1.44, 10.32)	0.14
3 months	n=31, 79.31 (11.77)	n=31, 82.39(14.24)	4.88	(-0.26, 10.02)	0.06
6 months	n=30, 82.77 (9.04)	n=33, 82.15(12.27)	1.19	(-3.96, 6.34)	0.66
12 months	n= 32, 78.66 (21.19)	n= 33, 79.12(16.90)	2.65	(-7.10,12.39)	0.59

Legend: n=numbers, CI=95% confidence interval of the difference. Summary measures are means and (SD) analysed using independent samples t test and treatment effects (difference between active and placebo treatments) are derived from univariate ANCOVA adjusted for baseline value, age, gender and BMI.

### 8.1.17.3 Short Form 36

Short form 36 (SF36) was analysed in each of its eight domains and the results are presented in Appendix 11.23 for each domain, other than the two which showed a statistically significant result, the SF 36 BP detailed in the pain section above (8.3.7.2) and SF 36 Physical Functioning below. Further analysis investigated the physical component scores and the mental component scores as a summary measure together.

### 8.1.17.4 SF36 – Physical Functioning

Both treatment groups showed an improvement in physical functioning as measured by the SF36 physical function score over the 12 month period. There was a statistically significant difference between the two groups in favour of the treatment group at six months ( $p=0.029$  95%CI=-0.01 to 0.38). Table 8.11 details the SF 36 Physical Functioning scores across all time points for both groups.

Table 8.11 SF 36 Physical Functioning across all assessment points

Time point	Placebo	Treatment	Treatment effect (95% CI)	P value
Baseline	n=35, 65.86 (20.77)	n=38, 68.16(23.20)		
2 months	n=32, 76.72 (19.90)	n=36, 78.47(19.00)	1.64 (-5.57, 8.85)	0.65
3 months	n=31, 74.19 (20.86)	n=31 83.23(15.84)	5.13 (-1.72, 11.99)	0.14
6 months	n=30, 77.50 (18.65)	n=32, 84.84(12.15)	7.95 (0.86, 15.04)	0.029
12 months	n= 32,79.38 (19.71)	n= 32,79.69(23.35)	-1.49 (-11.78, 8.81)	0.77

Legend: n=numbers, CI=95% confidence interval of the difference. Summary measures are means and SD analysed using independent samples t test and treatment effects (difference between active and placebo treatments) are derived from univariate ANCOVA adjusted for baseline value, age, gender and BMI. Scores are an aggregate percentage where 0= worst possible functioning and 100=best.

#### 8.1.17.5 SF 36 – Summary measures

##### 8.1.17.5.1 Physical component summary (PCS)

Both treatment groups demonstrated a statistically significant change from baseline to two months (placebo mean difference= -6.82, 95%CI=-8.97, -4.66, p=0.00, long-chain omega-3 PUFA mean difference= -5.38, 95%CI=-7.68, -3.07, p=0.00). This was not continued at 12 months with neither group showing a statistically significant change between two and 12 months (placebo, -2.61, 95%CI=-6.94, 0.91, p=0.14, long-chain omega-3 PUFA mean difference=-0.19, 95%CI=-3.77, 3.39, p=0.91).

There were no between group differences observed across all time points (two months, mean difference= -0.73, 95%CI= -4.94, 3.76, p=0.79; 12 months mean difference= -0.59, 95% CI= -4.94, 3.76, p=0.79).

There were no significant differences found for the change in SF 36 physical component summary score between groups using a mixed model analysis up to 12 months (p=0.77).

Table 8.12 details the SF 36 Physical Component scores across all time points for both groups.

Table 8.12 SF 36 Physical component summary (PCS) across all assessment points

Time point	Placebo	Treatment	Treatment effect (95% CI)	P value
Baseline	n=35, 37.95 (8.18)	n=38, 41.54 (8.26)		
2 months	n=32, 45.55 (8.16)	n=36, 46.77 (8.77)	-0.40 (-3.36, 2.56)	0.79
3 months	n=31, 43.20 (8.42)	n=31, 48.02 (8.76)	1.07 (-2.27, 4.41)	0.52
6 months	n=30, 47.06 (6.61)	n=32, 47.60 (11.39)	-0.45 (-5.36, 4.46)	0.86
12 months	n= 32, 47.62 (8.92)	n= 32, 49.14 (8.85)	-0.44 (-5.00, 4.13)	0.85

Legend: n=numbers, CI=95% confidence interval of the difference. Summary measures are means and SD analysed using independent samples t test and treatment effects (difference between active and placebo treatments) are derived from univariate ANCOVA adjusted for baseline value, age, gender and BMI. Scores are an aggregate percentage where 0= worst possible functioning and 100=best.

#### 8.1.17.5.2 Mental component summary (MCS)

Neither group showed a statistically significant change at two months (placebo mean difference= 2.38, 95%CI= -0.19, 4.95, p=0.07, long-chain omega-3 PUFA mean difference= -1.53, 95%CI= -4.90, 1.84, p=0.49) or 12 months (placebo mean difference= 0.31, 95% CI=-2.70, 3.33, p=0.83; long-chain omega-3 PUFA= 0.92, 95%CI=-2.96, 4.80, p=0.63).

At baseline there was a statistical difference between groups with the placebo group starting with a higher score, better functioning metal component (mean difference=5.03, 95% CI =0.74, 9.32, p=0.02). Following this there were no between group differences in the remainder of the study period (two months; mean difference= 2.86, 95%CI= -2.24, 5.96, p=0.37; 12 months mean difference= 0.59, 95%CI=-3.33, 4.52, p=0.76)

There were no significant differences found for the change in SF 36 mental component summary score between groups using a mixed model analysis up to 12 months (p=0.83). Table 8.13 details the Mental Component Summary scores across all time points for both groups.

Table 8.13 SF 36 Mental component summary (MCS) scores across all assessment points

Time point	Placebo	Treatment	Treatment effect (95% CI)	P value
Baseline	n=35, 54.67 (8.03)	n=38, 49.64 (10.13)		
2 months	n=32, 52.44 (8.82)	n=36, 50.93 (10.70)	1.90 (-2.25, 6.01)	0.36
3 months	n=31, 55.94 (6.15)	n=31, 52.96 (8.69)	-0.40 (-3.76, 2.97)	0.82
6 months	n=30, 54.20 (7.13)	n=32, 51.13 (9.46)	-0.31 (-4.05 3.43)	0.87
12 months	n=32, 52.65 (8.42)	n=32, 50.80 (9.94)	1.52 (-2.36, 5.40)	0.45

Legend: n=numbers, CI=95% confidence interval of the difference. Summary measures are means and SD analysed using independent samples t test and treatment effects (difference between active and placebo treatments) are derived from univariate ANCOVA adjusted for baseline value, age, gender and BMI. Scores are an aggregate percentage where 0= worst possible functioning and 100=best. Treatment effect is the difference between active treatment and placebo.

#### 8.1.18 GLOBAL PERCEPTION OF CHANGE

Both groups reported a greater than 50% improvement over the intervention. There was no statistical difference between the groups of the level of perceived change across all time points (three months, mean difference=5.72, 95%CI= -4.32, 15.75, p=0.26, 12 months, mean difference=-2.56, 95%CI=-15.73, 10.61 , p=0.70).

Twenty six percent of participants at 12 months rated their improvement as being 100% and 58% rated their improvement as 90% or better. Table 8.15 details the Global Perception of Change scores across all time points for both groups.

Table 8.14 Global perception of change scores across all assessment points

Time point	Placebo	Treatment	Treatment effect (95% CI)	P value
2 months	n=33, 54.09 (30.12)	n=37, 55.27 (30.73)	-0.05(-14.91, 14.82)	0.10
3 months	n=31, 66.13(22.29)	n=31, 70.81 (25.27)	7.00(-5.60, 19.60)	0.27
6 months	n=30, 75.57 (20.57)	n=33, 74.18(32.29)	-2.01(-16.60, 12.59)	0.78
12 months	n= 32, 80.00 (22.51)	n= 33,77.97 (32.58)	-1.33(-16.01, 13.35)	0.86

Legend: n=number, 95% CI=95% confidence interval of the difference. Summary measures are means and SD (95% confidence intervals) analysed using independent samples t test and treatment effects (difference between active and placebo treatments) are derived from univariate ANCOVA adjusted for baseline value, age, gender and BMI.

### 8.1.19 IMPAIRMENT MEASURES

#### 8.1.19.1 Range of motion

A statistically significant improvement was observed across both groups within the 12 months ( $p \leq 0.02$ ) for all range of motion measurements other than shoulder joint abduction in the placebo group ( $p=0.06$ ).

The results showed statistically greater improvement in symptomatic shoulder flexion and abduction range at three months in the treatment group when compared to the placebo group (for flexion mean difference = 7.71, 95%CI= 2.37, 12.86,  $p=0.01$ , for shoulder abduction, mean difference=10.41, 95%CI= 3.12, 17.70,  $p=0.01$ ). There were no statistically significant differences in the other movements of shoulder external rotation or hand behind back (Table 11.24 in Appendices).

#### 8.1.19.2 Strength

A statistically significant improvement was observed across both groups within the 12 months ( $p \leq 0.03$ ) for all strength measurements other than elbow flexion in the placebo group ( $p=0.11$ ).

No statistically significant differences were observed between the groups in all strength measurements over all time points, other than shoulder external rotation at 12 months (mean

difference= -0.94, 95%CI=-4.16, 2.27, p=0.01). Whilst this is a statistically significant difference in favour of the treatment group, it is not believed to be clinically significant. These results indicate that shoulder strength measures were unaffected by the type of supplement taken (Table 11.25 in Appendices).

### 8.1.20 Dietary intake of study participants

The dietary intake of the participants analysed from the data provided in their four day food diaries is detailed in Table 8.15. The estimated nutrient intake from the four day food diaries completed at baseline and trial end point (12 months) and were analysed for consistency of nutrient intake over the trial period. There were no statistically significant differences in pre and post-trial fatty acid intakes for the participants. However there were significant differences in intake in zinc, folate and vitamin A between the two groups.

This data is also compared to the data published in the national average taken from the National Diet and Nutrition Survey (Public Health Engand 2014) (table 8.16).

Table 8.15 Dietary intake of study participants

	<b>Placebo (n=30)</b>	<b>Treatment (n=31)</b>	<b>Mean Difference (95%CI adjusted for baseline)</b>	<b>P value of the difference</b>
<b>Energy (MJ/day)</b>				
Baseline	7.48 (2.08)	7.31 (2.12)		
1 year	6.90 (2.17)	7.09 (2.03)	0.78 (-0.82, 1.46)	0.57
<b>Protein (% energy)</b>				
Baseline	17.02 (2.81)	17.66 (4.13)		
1 year	17.34 (3.38))	18.50 (3.91)	0.16 (-0.68, 3.08)	0.21
<b>CHO (% energy)</b>				
Baseline	42.00 (9.28)	44.57 (8.48)		
1 year	40.57 (8.15)	42.56 (8.81)	-0.10 (-6.26, 3.04)	0.49
<b>Fat (% energy)</b>				
Baseline	36.58 (7.38)	36.00 (7.64)		
1 year	37.58 (6.35)	36.04 (7.47)	-0.06 (-4.77, 3.15)	0.68

<b>SFA (% energy)</b>				
Baseline	13.97 (5.66)	13.26 (4.30)		
1 year	15.16 (6.23)	14.22 (6.02)	-0.03 (-3.54, 2.87)	0.84
<b>MUFA (% energy)</b>				
Baseline	11.66 (3.02)	11.73 (3.70)		
1 year	11.16 (2.59)	10.58 (2.90)	-0.06 (-1.88, 1.19)	0.65
<b>PUFA (% energy)</b>				
Baseline	6.01 (2.01)	5.90 (2.07)		
1 year	6.86 (3.17)	6.42 (3.64)	0.03 (-1.92, 2.26)	0.87
<b>Omega-3 PUFA (g/day)</b>				
Baseline	0.06 (0.18)	0.06 (0.18)		
1 year	0.07 (0.16)	0.24 (0.57)	0.19 (-0.11, 0.45)	0.23
<b>EPA (g/day)</b>				
Baseline	0.02 (0.05)	0.02 (0.08)		
1 year	0.02 (0.03)	0.05 (0.13)	0.14 (-0.04, 0.09)	0.36
<b>DHA (g/day)</b>				
Baseline	0.01 (0.06)	0.03 (0.10)		
1 year	0.03 (0.08)	0.08 (0.31)	0.12 (-0.09, 0.21)	0.46
<b>Dietary fibre (g/d)</b>				
Baseline	16.72 (7.09)	18.80 (7.51)		
1 year	13.87 (4.46)	16.59 (5.75)	0.15 (-1.23, 4.43)	0.26
<b>Potassium (mg)</b>				
Baseline	2696.17 (782.38)	2770.4800 (907.05)		
1 year	2403.37 (675.96)	2695.20 (880.15)	0.21 (-101.48, 769.32)	0.13
<b>Calcium(mg)</b>				
Baseline	707.43 (213.41)	653.80 (234.56)		
1 year	716.05 (289.21)	683.17 (320.80)	0.22 (-158.81, 185.95)	0.87
<b>Iron(mg/d)</b>				

Baseline	10.38(3.69)	10.31 (4.18)		
1 year	9.07 (3.71)	10.48 (3.00)	0.24 (-0.33, 3.57)	0.10
<b>Zinc(mg/d)</b>				
Baseline	8.21 (2.80)	8.00 (3.07)		
1 year	7.20 (2.30)	8.57 (2.69)	0.31 (0.13, 3.11)	0.03*
<b>Thiamin (mg/d)</b>				
Baseline	1.37 (0.42)	1.38 (0.58)		
1 year	1.27 (0.46)	1.38 (0.46)	0.15 (-0.13, 0.41)	0.31
<b>Riboflavin (mg/d)</b>				
Baseline	1.50 (0.83)	1.42 (0.74)		
1 year	1.39 (0.53)	1.43 (0.67)	0.10 (-0.23, 0.48)	0.49
<b>Niacin (mg niacin equivalents/d)</b>				
Baseline	33.11 (3.21)	33.50 (13.03)		
1 year	32.43 (12.43)	33.08 (12.97)	0.09 (-4.26, 8.66)	0.50
<b>Folate (µ g/d)</b>				
Baseline	204.50 (73.41)	211.77 (94.63)		
1 year	188.37 (57.79)	217.88 (88.54)	0.27 (4.07, 78.80)	0.03*
<b>B12</b>				
Baseline	5.83 (9.13)	4.17 (2.69)		
1 year	4.16 (2.38)	6.68 (2.71)	0.11 (-1.00, 2.18)	0.51
<b>Vitamin A (retinol equivalents/d) (µ g/d)</b>				
Baseline	2796.09 (1351.99)	2585.29 (1595.22)		
1 year	2222.89 (955.50)	3590.83 (2839.86)	0.31 (148.17, 2679.90)	0.03*
<b>Vitamin D (µ g/d)</b>				
Baseline	1.80 (1.38)	2.13 (2.52)		
1 year	2.72 (2.73)	2.63 (2.17)	-0.27 (-1.63, 1.38)	0.86

Legend: CI=95% CI, CHO=carbohydrate, EPA= eicosapentaenoic acid, DHA= docosahexaenoic acid, SFA=saturated fatty acid, MUFA=monounsaturated fatty acid, PUFA= polyunsaturated fatty acid.



From the values below (Table 8.16) the dietary intake of the study participants' was largely in line with the national average.

Table 8.16 Mean dietary intake of study participants as compared to national average values

	Trial participants (N=61)		National Diet & Nutrition survey		P-value
	Men (n=30)	Women(n=30)	Men	Women	
Mean energy (MJ)					
19-64 years	7.758 (2.00)	7.403 (1.83)	8.88	6.78	0.99/0.99
65 & over	8.197 (2.52)	8.845 (0.71)	8.14	6.35	0.99/0.75
Protein (% energy)	17.667% (3.92)	16.309% (2.59)		17.50%	0.82
CHO (% energy)	39.432% (8.39)	46.943% (8.00)		47.20%	0.47
Fat (% energy)	37.156% (7.22)	35.588% (7.40)		35.50%	0.72
SFA (% energy)	13.937% (4.26)	12.254% (3.81)		13.20%	0.98
MUFA(% energy)	12.808% (2.87)	11.566% (3.31)		12.50%	0.81
PUFA (% energy)	6.037% (1.69)	6.316% (2.16)		5.50%	0.87

Legend; CHO=carbohydrate, SFA=saturated fatty acid, MUFA=monounsaturated fatty acid, PUFA= polyunsaturated fatty acid.

#### 8.1.21 Consistency of exercise class at each site

Observation of the shoulder classes periodically at all sites confirmed that all groups continued to run as described in Chapter 5 (5.3.3.8.2).

### **8.1.22 Quality control of PUFA supplements**

A sample of the long-chain omega-3 PUFA supplements were returned to Seven seas for analysis after the last participant had finished the intervention period. The supplements were analysed for any oxidation and levels of EPA and DHA. The results showed no oxidation had occurred outside expected limits and the content of the supplements remained unchanged (Appendix 11.17).

### **8.1.23 Adverse events**

No serious adverse events were reported. Two participants (*39 and 61*) stopped taking the capsules due to issues with indigestion or upset stomach. The participant information sheet stated “reported side effects have included an upset stomach or stomach pain, black tarry stools, bruising and heartburn”. Three participants reported that they were unable to take the full number of capsules each day due to feeling uncomfortable or having difficult taking the capsules (*Participants 25, 72 and 75*). Others reported feelings of heartburn or nausea but reported continuing to take the full number of capsules each day.

### **8.1.24 Sensitivity analysis**

The study was powered taking into account a 10% drop out but only a 4% drop out was observed at the primary outcome point. Given this low rate no multiple imputation methods were needed and no sensitivity analysis was indicated.

The data was explored as a post hoc analysis to see if there were any statistically significant differences between those who ‘adhered’ to the long-chain omega-3 PUFA supplements and those who did not. When a level of 4.2 percentage weight total long-chain omega-3 PUFAs is applied as the cut off point for adherence in the post supplementation plasma fatty acid analysis, a similar picture is seen as in the intention to treat analysis in the primary and secondary outcome measures. Similarly missing number imputation does not produce any statistically significant results in the primary outcome measure for either group across all time points.

#### **8.1.24.1 Does level of EPA and DHA in plasma correlate to an improvement in OSS, SPADI, NRS or SF36 bodily pain outcomes?**

A post hoc analysis of the effect of increased EPA and DHA within the plasma and the improvement in disability and pain at the primary outcome point of two months using regression and (partial correlations), adjusted for treatment group was conducted. There was

no evidence within this sample that there is a relationship between EPA and DHA plasma levels and reduction in disability as measured by the OSS and SPADI. However a relationship between increasing EPA and DHA plasma levels and decreasing reported pain as measured by the NRS was found (correlation= -31% for EPA and 32% for DHA,  $p=0.01$  for both EPA and DHA). For each unit increase of EPA and DHA there was on average a 9% and 14% change observed in the NRS score respectively.

#### **8.1.25 Summary**

From the results presented in the study sample, we observed that there was no statistical difference detected between the two groups over each time point up to 12 months, suggesting that no added benefit was afforded by taking the PUFA supplement in terms of disability as measured by the primary outcome. There was a statistically significant difference between the two groups in disability as measured by the SPADI in favour of the treatment group at three months but this benefit had disappeared by 12 months. This might suggest that the addition of a PUFA supplement might improve speed of recovery of function between two and six months.

There was a statistically significant difference found at 12 months in the treatment group with regards to pain measured by the SF 36 BP component and at three months as measured by the SPADI pain sub scale. This finding was not supported by the other two pain measurement outcomes.

## **Discussion**

This study set out to compare the efficacy of long-chain omega-3 PUFA supplements to a placebo supplement in the treatment of RC tendinopathy. This study demonstrated that individuals with RC tendinopathy who participated in an eight week exercise class and took either long-chain omega-3 PUFA supplements or placebo supplements reported statistically significant improvements in disability (as measured by the OSS) at two months, three months, six months and one year. Improvement in disability was similar in both supplement groups. These results provide insufficient evidence to reject the null hypothesis that there is no difference between the two treatment groups at two, three, six or twelve months.

There was a clinically and statistically significant reduction in pain and disability score in both groups. The mean increase in the OSS score in the long-chain omega-3 PUFA group was 6.65

points and the corresponding result in the placebo group was 8.22 points at two months, both groups achieving the MICD (van Kampen, Willems et al. 2013). When reviewing results from the one of the secondary outcome measures, the SPADI, the long-chain omega-3 PUFA group achieved a more rapid improvement in disability than the placebo group. The long-chain omega-3 PUFA group demonstrated a 64% improvement from baseline at three months, compared to a 42% in the placebo group, which had then equalled out by the six month assessment.

#### **8.1.26 Baseline demographic data**

Participants who consented and took part in this study were typically in their 50<sup>th</sup> decade (mean age 52.14 years, SD = 14.06) and were evenly distributed between men and women. This demographic presentation is typical of other RC populations in clinical trials in the UK and Scandinavia (Ketola, Lehtinen et al. 2013, Kukkonen, Joukainen et al. 2014, Littlewood, Malliaras et al. 2014). Baseline OSS scores of 32 in the current trial were slightly higher (indicating less severe disability) than other published RC tendinopathy trials (Ainsworth, Lewis et al. 2009) but similar to others (Ekeberg, Bautz-Holter et al. 2010, Younis, Sultan et al. 2011). The baseline SPADI scores of 41 were similar to other RC tendinopathy trials (Engebretsen, Grotle et al. 2009, Yiasemides, Halaki et al. 2011, Kromer, de Bie et al. 2013). The similarity in the baseline level of disability as measured by OSS and SPADI compared to other trials, indicates the level of disability and demographics are suitably representative of the RC tendinopathy population within the UK and Scandinavia that have participated in research investigations. The average body mass index of the participants in this study was 28.15 which is categorised as overweight, and 70% of participants were classed as overweight (BMI of 25-30) or obese (BMI of  $\geq 30$ ). However this is reflective of in the general population with 50-60% being classed as overweight or obese within this age range (Public Health Engand 2014).

The mirroring of the characteristics of the general RC tendinopathy population within the UK allows the generalisation of the findings of this study with more certainty to the wider RC tendinopathy population.

Participants were recruited from four NHS physiotherapy sites located across London. These locations included both suburban and inner city sites. This range in recruitment locations

encouraged a diverse study population which would be representative of the country as a whole, allowing wider generalisation of any results across the UK.

#### **8.1.27 Participation and attrition**

Retention was excellent throughout the study with 96% retention (70/73) at primary outcome point of two months and 89% retention (65/73) at one year. This compares favourably with other trials conducted on similar RC tendinopathy populations (Lewis 2012, Littlewood, Bateman et al. 2016).

The sample size calculation identified that 29 participants were required in both groups. The required numbers of participants were reassessed at both the primary and end outcome points, thereby reducing the risk of a type two error or false negative due to underpowered sample groups.

Although not significant a slightly larger proportion of participants not completing the study at one year had been allocated to the placebo group. There was a higher level of disability in the non-completers at baseline and subsequent attrition may have affected outcome. However percentage of non-completers was so low it is probable that any effect would be negligible.

#### **8.1.28 Reasons for clinical outcomes and explanation of results**

Regression to the mean is a statistical phenomenon which describes the tendency for extreme symptoms at baseline to return to a more central distribution on follow up and final assessments (Morton and Torgerson 2005).

Individuals with chronic musculoskeletal conditions such as RC tendinopathy tend to seek help, treatment and enrol in research at the peak of their symptoms. Natural improvement most usually follows and post intervention or final assessment scores will often have improved, even if therapy is ineffective (Krogsboll, Hrobjartsson et al. 2009). The effect of regression to the mean was minimised within this study through random allocation, the use of multiple baseline measurements and the analysis of the data with ANCOVA, which adjusts for baseline value of each variable (Barnett, van der Pols et al. 2005).

In this study, the greatest change in reduction in disability occurred at two months from baseline. During this time participants completed the intervention, the exercise class, home

exercise programme and supplements for two months. Both groups also showed an improvement in reported disability at three, six and twelve months when compared to the baseline. This improvement might reflect natural recovery of RC tendinopathy. Due to the lack of a non-treatment group it is not possible to determine how much of the change reported at the outcome points was due to regression to the mean, natural recovery, the immediate or longer term effects of attending an exercise class and home exercises, or the immediate or longer term influence of the supplements. However natural recovery is unlikely to account for the whole effect observed in the cohort given the long duration of symptoms and the moderate disability at baseline, both of which have been associated with a poorer prognosis (Kuijpers, van der Windt et al. 2004, Thomas, van der Windt et al. 2005). In addition, minimal improvements in pain and function have been observed in other studies with participants with RC tendinopathy over similar duration and with control groups receiving no intervention (Ludewig and Borstad 2003, Lombardi, Magri et al. 2008, Clement, Nie et al. 2012).

Another contributing factor to a patient's outcome is the placebo effect (Barker, Pistrang et al. 2002). The placebo effect is a commonly recognised phenomenon and is defined as the psychological or physiological effect of an inert intervention which is designed to have no specific effect other than satisfying the patient (Price, Finniss et al. 2008). The placebo effect is thought to contribute approximately 30% and spontaneous recovery 10% of total outcome of an intervention for a chronic pain condition (Krogsboll, Hrobjartsson et al. 2009). The placebo effect has been reported to have the greatest influence over pain patient reported outcomes (Hrobjartsson and Gotzsche 2001, Hrobjartsson and Gotzsche 2004).

In this study there was a blinded placebo supplement control group which was used as a comparison with the long-chain omega-3 PUFA supplement intervention group. The allocation of a supplement to the control group (as compared to a control group not taking any supplement) aimed to reduce the possibility that any positive study findings were related to the influence of the placebo effect of being provided with supplements rather than any potential benefits of the long-chain omega-3 PUFA components of the supplements. However, the equivalent improvement in both the treatment groups may in part have been attributable to a placebo effect.

Changes in psychological or social factors might also explain the similar clinical outcomes between the treatment groups in this study. The shoulder exercise group educated

participants in the importance of exercise and relaxation, pain management and their condition. In addition, participants in the study had more regular follow up and reassessment for a longer duration than 'normal' treatment. During these follow up visits the participants were encouraged to continue with their exercise programme and any questions answered. They would also be given an indication of any improvement. Improved coping strategies (Minns Lowe, Moser et al. 2014) have been reported to improve clinical outcome for RC tendinopathy and higher levels of therapist supervision has been shown to have a positive influence on reduction in pain in low back pain exercise treatment (Reilly, Lovejoy et al. 1989).

#### **8.1.28.1 Aspects of the interventions**

##### **8.1.28.1.1 Content of long-chain omega-3 PUFA supplement**

It is possible that the long-chain omega-3 PUFA supplement provided at the 9g/d dose was inadequate to appropriately influence the proposed inflammatory mechanisms and the symptoms of RC tendinopathy. The dosage of long-chain omega-3 PUFA and GLA was higher in the studies conducted both by Mavrogenis et al (2004) and Roe et al (2005). Whilst positive effects were noted at that dose given in the Mavrogenis et al (2004) experimental group, similar outcomes were not observed in study conducted by Roe et al (2005). The relationship observed in this study with EPA and DHA and pain (as measured by NRS) would lend weight to the argument of investigating the efficacy of higher doses of long-chain omega-3 PUFA. However caution must be taken when looking at the results of the association of EPA and DHA with pain. It may be a case of multiplicity where if hypotheses are tested on different subsets of the data, the likelihood that some will appear falsely positive may increase (Lord, Gebiski et al. 2004).

The literature regarding what dosage is required is unclear (4.2.4) and the dose selected in this study chosen on the basis it was at the lower limit of that which might elicit an anti-inflammatory effect but not high enough to cause gastro-intestinal problems.

Compliance to the intervention was generally good with good corroboration between reports of the number of capsules taken and the number of capsules returned. Independent verification that the participants were taking the supplements was provided by the significant increases in the proportions of EPA and DHA in plasma lipids. Furthermore, there was no evidence that dietary intake of the participants changed over the period of the study. There were, however, considerable variations in the size of the increases in EPA and DHA within the

participants allocated to the long-chain omega-3 treatment and this may reflect differences in body size as well as the intake of other fatty acids particularly omega-6 fatty acids in the background diet. High intakes of linoleic acid have the effect of reducing the incorporation of EPA and DHA into phospholipids and cholesterol esters which are major lipid classes in plasma total lipids. The increases in EPA and DHA are comparable with other studies that have used intakes of long-chain omega-3 PUFA in the range of 2-3g/d. MaxEPA which was used in the present study contains in total approximately 35% long-chain omega-3 fatty acids (including 18:4n-3, 20:4n-3, 22:5n-3), with EPA and DHA typically providing 18% and 12% of the fatty acids. Allowing for the non-fatty acid components, the calculated intake of total long-chain omega-3 fatty acids would be close to 3g/d. This is the level where triglyceride lowering effects are noted as well as effects on blood pressure. Even if an allowance is made for incomplete consumption (eight versus nine capsules/d), this still would provide an intake of 2.7g/d of long-chain omega-3 fatty acids. While higher intakes of long-chain omega-3 PUFAs might have anti-inflammatory effects, the safety of higher intakes taken for long-periods of time is less well established. The findings of this study, therefore, are relevant to clinical practice.

Both the placebo and long-chain omega-3 PUFA supplements contained the same amount of antioxidants per capsule and the intake of nine capsules per day would have equated to; 12mg tocopheryl acetate (vitamin E), 270 µg retinol equivalents Vitamin A and 2.25 µg vitamin D. These values are well below the reference nutrient intake (RNI) for adults of vitamin A (600µg retinol equivalents for women and 700µg for men) and the food labelling recommended daily allowances (RDA). Most adults depend on exposure to sunlight for vitamin D but the Department of Health has recently proposed that all adults should have 10µg vitamin D/d in winter months which is an intake unlikely to be achieved without supplementation. The UK has no RNI for vitamin E but the for the European Nutritional Labelling Directive species as reference intake of 12mg/d. What is unknown is the contribution of the vitamin E, D and A to the overall treatment effect in this study as there was no arm without supplementation.



#### **8.1.28.1.2 Content of the placebo supplement**

The placebo capsules contained inert oil (refined olive oil British Pharmacopeia (BP) specification) and the same anti-oxidants as in the active capsules. The major fatty acid in the placebo was oleic acid. The intake of this fatty acids would be no more than 5g greater than in the active capsules. Oleic acid typically accounts for 12% of the dietary energy intake which on 2000 kcal/d is 27g/d. Consequently, the increase in oleic acid intake attributable to the supplements would be estimated to be small (2% energy). Most studies using MaxEPA have used olive oil- BP as a placebo and while health claims have been made for virgin olive oil (Buckland and Gonzalez 2015), these are attributed to non-fatty acid components which are present in much lower quantities in the British Pharmacopeia specification than in refined olive oil.

Whilst it is unlikely, it is not known whether or not the contents of the placebo capsules contributed to the overall treatment effect, due to the lack of a no supplement arm.

#### **8.1.28.1.3 Duration of treatment**

It is possible that the duration of the treatment was also not sufficient to achieve clinically significant results. Two months supplementation was selected on the duration in previous trials and evidence suggesting that there is a maximal incorporation into the plasma phospholipids at four weeks (Healy, Wallace et al. 2000, Yaqoob, Pala et al. 2000). The positive results reported by Mavrogenis et al (2004) were seen at 32 days, which was half the duration of the intervention and first outcome point of the current study. It is however common in trials of long-chain omega-3 PUFAs for the treatment of the symptoms of rheumatoid arthritis and osteoarthritis, for supplementation to last up to six months in duration. It is not possible to say whether ongoing supplementation would have afforded any additional benefit in this study.

#### **8.1.28.1.4 Adherence to treatment**

The adherence rate within this study was evaluated using return capsule count, total plasma lipid analysis, diary recollections and attendance to shoulder class group. The capsule counts indicated that 61% of participants consumed >90% of the capsules provided. This is lower than other trials investigating efficacy of long-chain omega-3 PUFAs (Sanders, Hall et al. 2011). However the mean (92%) and median capsule counts (97%) compare favourably to other reported efficacy trials (Kremer, Lawrence et al. 1990). No adherence rates with the

supplementation were given by either of the previous studies investigating the efficacy of long-chain omega-3 PUFAs and tendinopathy (Mavrogenis, Johannessen et al. 2004, Roe, Odegaard et al. 2005).

The adherence rate to the exercise class was not significantly different between groups ( $p=0.10$ ) and so any influence of non-adherence is likely to have been present equally in both groups. The mean adherence rate to the shoulder exercise class across the groups was placebo group (mean= 6.58 classes, SD= 2.06, 82% attendance) and the long-chain omega-3 PUFA group (mean= 5.73 classes, SD= 2.73, 67% attendance). This is similar to reported adherence with a self-management programme for RC tendinopathy (adherence rate=78%, although adherence data was only available on 29% of participants) (Littlewood, Bateman et al. 2016). When the percentage of participants completing all eight shoulder classes offered (overall=37%; placebo group = 46%, treatment group= 11%) the adherence rate to the classes is comparatively low to other adherence rates for shoulder exercise classes (92% (Bennell, Wee et al. 2010)). The low level of attendance to all eight classes offered when compared to the placebo group may have introduced a masking effect on any benefit the long-chain omega-3 supplements may have had.

#### **8.1.28.1.5 Inclusion of exercise**

The primary outcome point and first follow up occurred at eight weeks. During this time participants attended up to eight shoulder exercise groups. Improvement in disability has been documented following such an exercise programme for a median of eight and a half weeks (Bang and Deyle 2000, Haahr and Andersen 2006, Ketola, Lehtinen et al. 2009, Kuhn 2009, Ketola, Lehtinen et al. 2013, Kukkonen, Joukainen et al. 2014, Littlewood, Malliaras et al. 2014, Littlewood, Bateman et al. 2016).

Improvement in disability associated with attendance to the exercise group may have overshadowed any change in disability directly associated with long-chain omega-3 PUFA supplement use. However, a well-structured exercise programme is the current best practice intervention for those with RC tendinopathy (Lewis, McCreesh et al. 2015) and subsequently potentially unethical to withdraw this intervention.

#### **8.1.28.2 Appropriateness of outcome points**

The timing of the follow up assessments may have been a contributing factor in the results of this study. The primary outcome point was immediately after the intervention ceased (both the supplementation and the exercise class). It may also have been that any effect of the intervention (exercise and supplements) may take longer than two months to become beneficial. However, the data detail that there was rapid improvement in all outcomes scores in the first two months. Nevertheless, the effect of long-chain omega-3 PUFA supplementation would be expected to persist for at least a further month because the turnover of lipids in white blood cells, which are involved in inflammation, is slow. Kremer et al (1990) reported benefits in clinical measures for six weeks following discontinuation of long-chain omega-3 PUFA supplements and attributed this improvement to decreasing levels of IL 1 (Kremer, Lawrence et al. 1990).

#### **8.1.28.3 Appropriateness of primary outcome measure**

It is possible that the OSS which was the primary outcome in this study was not sensitive enough to detect any change attributable to the long-chain omega-3 PUFA supplements. A statistically significant difference in reduction in disability (as measured by SPADI) was seen at three months. However this was not mirrored in the OSS. This is in despite of reported good correlation between the OSS and SPADI (correlation coefficient= 0.85) and good agreement between the scores (weighted kappa=0.79) (Cloeke, Lynn et al. 2005). One reason for the difference in the scores of the SPADI and OSS at three months is the recall period stated by each of the different questionnaires. The SPADI asks the respondent to recall symptoms during the past week, whereas for the OSS the respondent recalls symptoms over the past four weeks. Between the primary outcome point at two months and the subsequent follow up at three months there was only a four week break. It is possible that any additional benefit that was experienced during the period between two and three months was not recorded by the OSS due to the recall period.

At the time the study was being designed, the OSS was commonly used clinically practice in the UK and in research and its use has been supported (Cloeke, Lynn et al. 2005). However Cloke et al (2005) reported that whilst their data support the use of the OSS, it also indicated that the SPADI might be preferable in terms of test-retest reliability. For each item within the questionnaires the weighted kappa coefficients were moderate to very good for the SPADI (0.51 to 0.80) but only fair to good for the OSS (0.13 to 0.78) (Cloeke, Lynn et al. 2005).

Subsequent research by Ekeberg et al (2008) has found the SPADI to be significantly ( $p<0.05$ ) more responsive than the OSS at two and six weeks using the standard response mean and reliable change proportion (Ekeberg, Bautz-Holter et al. 2008).

#### **8.1.29 Comparisons of findings to other studies**

The findings of the current study are in agreement with other similar studies, where one treatment approach has not been found to confer additional benefit to another in the treatment of RC tendinopathy (Ludewig and Borstad 2003, Faber, Kuiper et al. 2006, Bennell, Wee et al. 2010, Littlewood, Bateman et al. 2016).

Two previous randomised controlled trials investigating the efficacy of long-chain omega-3 PUFA supplements and tendinopathies have been identified (Mavrogenis, Johannessen et al. 2004, Roe, Odegaard et al. 2005). Mavrogenis et al. (2004) reported a significant improvement in pain after 32 days of supplementation with long-chain omega-3 PUFA and an antioxidant pill in a group of recreational athletes with a range of tendinopathies. This was a double blinded study and had a matched placebo control group; however the study is at risk of bias due to methodological flaws. Data analysis was not on an intention to treat basis and non-compliers were excluded from data analysis. In this study, 20 subjects were randomized to each group (40 in total), nine subjects were lost to follow-up (three in treatment group and six in placebo group), and final follow-up (subjective pain scores and estimated levels of sports activity) occurred at 32 days. The study group was comprised of tendon pathologies from different regions of the body including the shoulder, elbow, and knee. In the shoulder region, there were 12 subjects in total, ten were diagnosed as having supraspinatus tendinopathy (ten in total, with five in each group), and two as having infraspinatus tendinopathy (two in total, with both in the experimental group). In general, the regional tendon pathologies were not equally distributed between the two groups. No adverse effects were reported by any of the participants in their study. Nine subjects were excluded from the analysis due to non-adherence (defined as failure to document test medication taken or training activity carried out in their diary) or 'protocol violation'. This study provided a valuable insight in the potential of these compounds in the management of tendon pathology but it is not known if the benefit in the experimental group was due to the individually active substances or the combination with ultrasound therapy. It is also not known from this study if the beneficial effect was due to the PUFA or the antioxidants of the combination of both active substances.

Roe et al (2005) also investigated the efficacy of the same supplement from the same manufacturer at the same dose, but not for the same duration, as Mavrogenis et al (2004) they confined their investigation to people diagnosed with lateral epicondylitis. Their study design was a double blinded RCT with concealed allocation of 60 participants (55 completed). The participants were randomised to placebo or capsules containing the essential fatty acids (omega 3 PUFAs and omega 6 GLA) and antioxidant tablet for eight weeks. Both groups also received eight sessions of trigger point therapy (one per week) and a structured and graded home exercise programme of eccentric exercises, lasting for the whole study period (24 weeks). There were no statistically significant differences observed in pain reduction levels between groups at all time points ( $p=0.16$  at eight weeks and  $p=0.76$  at 24 weeks). There was a clinically meaningful mean reduction in pain in both groups on a 10cm VAS scale within both groups of 3cm (95%CI=2.5-4) at eight weeks which continued to reduce up to 24 week. Analysis was on a complete case basis and not on an intention to treat principal. The final follow up was at six months. There was a large variation in the duration of symptoms with those in the treatment group (18 months; SD=22 months) having a mean duration of symptoms twice as long as those in the placebo group (8 months; SD=4 months). The longer duration of symptoms in the treatment group is likely to be accompanied with a poorer prognosis (Bartolozzi, Andreychik et al. 1994). With such inequality in duration of symptoms at the start of treatment between groups it is not possible to draw definitive conclusions from this study.

Mavrogenesis et al (2004) reported a significant reduction in pain within the treatment group at four weeks but Roe et al (2005) found no added benefit of the essential fatty acid and antioxidant supplement at eight weeks. The dosage of EPA and DHA was twice as high in these two studies than in the current study (5.1g/day EPA and DHA versus 2.6g/day in the current study) and additionally contained 2.7g/d GLA. The participants in the Mavrogenis et al (2004) and Roe et al (2005) studies were also given an antioxidant tablet containing 100µg selenium, 15mg zinc, 1mg vitamin A, 2.2g vitamin B<sub>6</sub>, 90mg vitamin C and 15mg vitamin E. It is possible that the greater dose, the additional antioxidants and GLA might have been the reason for the decrease in pain scores observed in the Mavrogeneis et al (2004) study. However the same dosage was used in the Roe et al (2005) study for a longer duration and no additional benefit was observed in the treatment group within this study. Interestingly, there was a greater decrease in mean pain scores in the Roe et al (2005) study and Mavrogenis et al (2004) studies than that observed in the current study (5 VAS points, 3.2 VAS points and 2.2 NRS points

respectively). This may be reflective of the different tendinopathies (a wide range of chronic tendon disorders by Mavrogenis group and lateral epicondylitis by Roe group) being investigated in the studies, the different adjunct treatments (ultrasound by Mavrogenis et al (2004), and trigger point therapy and exercise used by Roe et al (2005) and the different pain measurement tools (VAS as compared to NRS, Mavrogenis et al (2004) and Roe et al (2005) respectively).

In addition, another reason for differing outcomes between the Mavrogenis et al (2004) and the current study and that conducted by Roe et al (2005) might be due to the longer duration of symptoms in the treatment groups of the current study (mean duration being nine months) and that of Roe et al (2005) (mean duration being 18 months) when compared to Mavrogenis et al (2004) (mean duration of symptoms being six months) with poor prognosis being associated with longer duration of symptoms (Bartolozzi, Andreychik et al. 1994). Disability scores were not assessed by either Mavrogenis et al (2004) or Roe et al (2005), subsequently further comparison between these studies cannot be made.

A thirty percent change in baseline OSS score was observed in the long-chain omega-3 PUFA group at three months within the current study. This is identical to the percentage change of OSS score from baseline observed in another study investigating the efficacy of an exercise programme for massive RC tears (Ainsworth, Lewis et al. 2009). The mean changes in SPADI scores at three months observed in this study are in agreement when compared to other studies investigating exercise for RC tendinopathy (Engebretsen, Grotle et al. 2009, Yiasemides, Halaki et al. 2011, Kromer, de Bie et al. 2013). The average reduction in SPADI scores in other investigation of RC tendinopathy and exercise in excess of 20 points at three months. In the current study the mean reduction in the treatment group at three months from baseline was 24.95 points.

This agreement in change in disability scores with previous studies investigating the efficacy of exercise for RC tendinopathies lends further evidence to support the current best practice treatment.

#### **8.1.30 Implications for clinical practice**

This is a novel exploratory study investigating the efficacy of long-chain omega-3 PUFA supplements and exercise in the treatment of RC tendinopathy. It provides clinicians with

evidence from a double blind randomised controlled trial. Based on the findings of this study, clinicians can feel confident that when advising patients with RC tendinopathy (who have the same clinical presentation as those in the current study) that at a similar dose of long-chain omega-3 PUFA to that given within this study (2.6g DHA and EPA, 9g/d of fish oil) and duration (eight weeks) that the supplementation does not afford any benefit over a placebo. The findings of this study also lend support to the argument that an exercise group plus a home exercise plan is an effective treatment in reducing pain and increasing function in those with RC tendinopathy.

### **8.1.31 Strengths and limitations**

#### **8.1.31.1 Use of self-report adherence measures**

One limitation of this study is that it was powered on only the primary outcome measure, the Oxford Shoulder Score, but several outcome measures were collected during the assessment process.

The intervention was given for a period of eight weeks and at a dosage of 3g long-chain omega-3 PUFA per day. These parameters were chosen based on the available research discussed in chapter 4. However it is possible that neither the dose given nor the duration of the treatment were sufficient to elicit a response and this would be an area warranting further research.

Within the statistical approach used in this study (ANCOVA) the data was adjusted only for the confounders collected including BMI, gender and age. However there may have been other confounders which were not collected and not adjusted for.

Olive oil was selected as the choice of placebo oil in this study as discussed in section 8.1.28.1.2 (pg 197). Health claims have been attributed to virgin olive oil (Buckland and Gonzalez 2015) however the olive oil used in this study was refined olive oil-British Pharmacopeia specification and the majority of the polyphenols (which might have a beneficial effect, yet to be proven) are removed in the refining process. A possible alternative placebo oil would be a mixed oil which reflects the background dietary fat intake of the participants and thus could not be suggested to attribute any added health benefits.

It is acknowledged that there was no wash out period for participants entering the trial who had previously been taking long-chain omega-3 PUFA supplements. This may have influenced the results however anyone already taking over 1g of long-chain omega-3 PUFA was excluded from entry into the trial.

Another limitation is the use of self-report measured of adherence to exercise and dietary surveys. It is recognised that patient self-report and completion of paper diaries can yield data of questionable validity (Stone, Shiffman et al. 2003). It is also acknowledged that the tendency to over-estimate adherence to a treatment is in the region of 10% (Moseley 2006). However this method was used in this investigation due to its practicality and limited resources available, such as no access to an electronic or online recording system. Adherence to the exercise class was also noted centrally and so whilst the amount of home exercise performed was also self-reported, the adherence to the shoulder exercise class was collected by the treating therapist. Similarly the diaries and the returned capsule count gave a self-report method of collecting data regarding adherence to the supplements; the total lipid analysis provided another measure of adherence which was not subject to potential bias. Interestingly, the number of capsules annotated as being taken in the diaries was on average less than the number calculated from the returned pill count, indicating that in this cohort of participants over estimation of the adherence to the supplements was not a feature.

Dietary surveys are reliant on self-reported food intake. Misreporting of food consumption, most often underreporting (either due to hide poor eating habits or make it simpler to record), in self-reported dietary methods is a well-documented issue (Black, Prentice et al. 1993, Livingstone and Black 2003). In order to overcome this we used a cut off of 1.2 for the ratio of reported energy intake to calculated basal metabolic rate (basal metabolic rate calculated using the Schofield equation)(Goldberg, Black et al. 1991). Using the 1.2 BMR cut-off suggests that 47% of the participants were under-reporting their dietary energy intake. However, in the case of micronutrient intake especially those which are found in a limited variety of foods such as calcium, vitamin D and long-chain omega-3 fatty acid under-reporting of energy intake is unlikely to be a problem particularly if the under-reporting of energy intake was from food with low nutrient density such as alcoholic drinks, confectionary and sugar sweetened beverages.



#### **8.1.31.2 Unmasking of group allocation**

Reassessment by the CI may have inadvertently resulted in unmasking of group allocation in a few cases due to comments made by the participants regarding 'fishy burps'. This may have introduced a risk of bias into the results. However, in an attempt to minimise any possible effect this might have had, no results were analysed until data from all participants had been collected.

#### **8.1.31.3 Multiple examiners**

First assessments and follow ups were not always conducted by the same examiner within the study. Having multiple examiners can introduce a measurement error. The reliability study indicated that the inter-tester reliability of the impairment measures methods was adequate. The primary outcome measure was the OSS which was a self-administrated questionnaire, and as such, it is unlikely that the results of the self-administered questionnaires would be influenced by a change in the examiner. There were different treating physiotherapists across the sites and over time but this is reflective of clinical practice.

#### **8.1.32 Further research**

Due to the design of this trial it is not possible to determine whether the use of either supplement resulted in an additional benefit in outcome above just attending the shoulder class. A similar trial comparing long-chain omega-3 PUFA with a placebo and no supplement would answer this question.

The use of biomarkers to assess the impact of the intervention on any inflammation in the rotator cuff or circulatory inflammatory markers would add a valuable insight.

Additional studies investigating if there are any effects of long-chain omega-3 PUFAs at differing higher doses, differing ratios of EPA versus DHA and longer durations would also allow the question of the efficacy of long-chain omega-3 PUFAs in the treatment of RC tendinopathy to be fully answered.

## **Conclusions**

This study is the first double blinded, randomised controlled trial with sufficient long term follow up to assess the efficacy of long-chain omega-3 PUFA supplements in the treatment of RC tendinopathy. The results of this study provide clinicians with evidence to advise and guide

patients that at 9g/d (2.6g EPA and DHA) for eight weeks, long-chain omega-3 PUFA provide no extra benefit for those with rotator cuff tendinopathy. In addition, the results also allow clinicians to be confident that following a well-structured exercise programme results in clinically meaningful changes in disability, function and pain.

#### Summary Points

- Change in self-reported pain and disability scores were similar between groups over all outcome points.
- It is also not clear from this study whether at a higher dose and/or for a longer duration long-chain omega-3 PUFAs might have an effect on disability and function in RC tendinopathy.
- A significant decrease in disability and pain as measured by the SPADI may indicate further research is warranted to explore this finding.
- The findings of this study indicate that for individuals with RC tendinopathy, long-chain omega-3 PUFA or a placebo supplement in addition to exercise would result in similar outcomes at one year.

**Chapter 9 : Exploring experiences,  
barriers, motivators and enablers to  
nutritional supplement use and  
exercise in rotator cuff  
tendinopathy: a qualitative study**

### **Authors Contribution to this study**

Fiona Sandford designed this study and devised the interview topic guide. She applied for ethical approval.

Fiona Sandford conducted all the interviews and transcribed them.

Jeremy Lewis and Fiona Sandford agreed themes from the transcripts.

Fiona Sandford further analysed the themes and illustrative comments for the discussion and prepared the findings for publication.

## **Introduction**

Exercise is the mainstay of physiotherapy treatment for rotator cuff (RC) tendinopathy (Littlewood, Ashton et al. 2012), often delivered in class based settings with home exercise plans in support. Little is known about the barriers, enablers and motivators in RC exercise based treatment. More is known regarding adherence to exercise in general but not in this cohort of patients. This study was designed to further explore this area.

The questionnaire based study presented in Chapter 8 indicates that nutritional supplements are being taken by a proportion of people seeking treatment for their shoulder pain within in the United Kingdom (UK). As part of the randomised controlled trial (RCT) study participants were asked to take nine capsules a day for two months. The various motivators, enablers and barriers have been further explored here. This study is complements the results presented in Chapter 7, the main RCT, and it is in part aimed at making the findings of the main RCT more clinically transferrable, aiding translation and relevance to clinical health communities.

There are several quantitative studies on exercise in RC tendinopathy (Bang and Deyle 2000, Haahr and Andersen 2006, Kuhn 2009, Kukkonen, Joukainen et al. 2014, Littlewood, Bateman et al. 2016) but those investigating qualitative aspects are lacking. Similarly there is limited published information relating to the experiences of individuals who have participated in an exercise class based programme as well as carrying out concomitant home exercises.

It is envisaged that through the identification of barriers to treatment adherence, clinicians may be able to develop and suggest methods to enhance adherence to exercise prescription for people with RC tendinopathy. This study also aimed to identify those barriers and highlight enablers or suggestions for strategies to overcome them.

Adherence is defined as “the act or quality of sticking to something.” (Ireland 2003). The word adherence has largely replaced the terms compliance and concordance in describing a patient’s disposition to follow precise instruction or prescribed treatment regimen. Compliance implies a more passive role by the patient whereas the word adherence carries with it more positive connotations and is more in line with the preferential collaborative approach where patients are actively involved in their management (Huss, Travis et al. 1997).

Adherence has been described as the “most unpredictable, least controllable variable in a medical intervention” (Groth and Wulf 1995). By its very nature clinical outcome is intrinsically linked to adherence (Abbott, Dodd et al. 1994, Groth and Wulf 1995, Ireland 2003). Non-adherence has been reported to attribute to the ongoing disability with subsequent or associated reduction in the ability to work and loss of wages (Kirwan, Tooth et al. 2002). Although studies have highlighted the importance of compliance or adherence in securing a successful outcome, in the clinical setting adherence is often erratic (Vermeire, Hearnshaw et al. 2001, Hayden, van Tulder et al. 2005). Adherence does not appear to be an all or nothing issue; rather it appears to be one of gradation, with some patients adhering to different degrees and with different components of treatment (Sluijs, Kok et al. 1993, Abbott, Dodd et al. 1994).

### **9.1.1 Aim of research**

The objective was;

To explore factors affecting adherence to a prescribed exercise programme and with the taking of the provided supplements.

The primary research question for this chapter was:

What are the enablers, barriers to adherence to an exercise based intervention and supplement prescription for RC tendinopathy?

### **9.1.2 Study design**

Qualitative methods were employed to explore factors affecting adherence to a prescribed exercise programme and with taking the provided supplements. These are further detailed in Chapter 5.3.6

### **9.1.3 Positionality of researcher**

The researcher was the chief investigator (CI) of a double blind placebo controlled RCT entitled: (The efficacy of polyunsaturated fatty acids and exercise in the treatment of RC tendinopathy. Trial registration: ISRCTN 17856844). The CI was responsible for recruiting, consenting and delivering the intervention for all the participants who then took part in this qualitative study. Within this qualitative study she developed the research protocol, recruited and consented the participants. She then conducted the interviews, transcribed the interviews, coded the transcripts and led the development of the themes from the data. Cross verification or researcher triangulation was achieved with a supervisor (JL) independently coding and analysing the transcripts and a consensus being reached as to the themes and sub-themes.

### **9.1.4 Ethics**

The original randomised controlled trial (The efficacy of polyunsaturated fatty acids and exercise in the treatment of RC tendinopathy ISRCTN 17856844) received ethical approval from Bromley Research Ethics Committee, Bromley Primary Care Trust, Bassetts House, Broadwater Gardens, Farnborough, Kent BR6 7UA (REC ref: 08/H0805/21) on 28<sup>th</sup> May 2008 (Appendix 11.13) and recruitment began in December 2008. The committee approved an amendment for this ancillary study on 12<sup>th</sup> September 2012 (Appendix 11.26), to collect

additional qualitative data via interviews with a sample of participants who had completed the original trial.

#### **9.1.5 Participants and recruitment**

A grounded theory approach was taken, with interviews conducted until theoretical saturation was reached (Glaser and Strauss 2009, Berterö 2012). A minimum of ten and a maximum of forty participants were sought to be interviewed, dependent on when theoretical saturation was achieved as well as resources available. Participants were purposively sampled from participants taking part in the RCT, to ensure the views of people from different age groups, gender and social backgrounds were captured. Participants who completed the main study between January 2012 and April 2013 (n=45) were approached by email, post or telephone and invited to attend for an interview at the Clinical Research Facility at St Thomas' Hospital, London, UK. All participants were interviewed at least one year after their randomisation into the trial.

All participants had been given the opportunity to attend eight RC exercises classes and been provided with eight weeks of supplements (either placebo or PUFA). As the group allocation code had not been broken at the time of the interviews it was not known whether or not the participant had been in the treatment or placebo group in the original trial.

##### **9.1.5.1 Inclusion criteria:**

- Consent to participate.
- Participated in the central study trial (The efficacy of polyunsaturated fatty acids and exercise in the treatment of RC tendinopathy ISRCTN 17856844).

#### **9.1.6 Consent and confidentiality:**

Participation in the interviews was entirely voluntary. The invitation to participate in the interviews was sent either by email or via letter through the postal service and was accompanied by an additional information sheet (Appendix 11.27) that explained the purpose of the interviews and potential benefits of participating in this investigation. A follow up phone call was organised to individual participants to explain the study further, to clarify any uncertainties and then ascertain if the participants would like to take part. Signed consent (Appendix 11.28) was obtained by the CI from those attending in person, before the interview commenced. Interview data was confidential and all information anonymised. The interviews



were recorded on two digital Dictaphones which were then transcribed and assigned an anonymised code to ensure no one was identifiable from the transcript. After transcribing, the recordings were destroyed.

#### **9.1.7 Data collection**

Interviews were conducted and transcribed by the CI. Further details can be found in Chapter 5.3.6.

#### **9.1.8 Interviews**

Face to face semi-structured interviews were conducted with the participants soon after they had completed the main study (The efficacy of polyunsaturated fatty acids and exercise in the treatment of RC tendinopathy) to explore their experiences during the year-long study.

An iterative research strategy was adopted, with open questions framed around the interview schedule/ topic guide (Table 9.1), starting with general questions which were then honed to more specific questions based on the responses of the participant but within the wider context of the research aims. Interviews took between 12-35 minutes each.

In developing the interview a deductive approach was taken, using topics generated from the CI's personal experience, reflection, as well as the literature. A list of topics to be explored was generated, from which questions were developed. At the start of each interview the participant was welcomed and thanked and this was followed by information provided by the CI of the participant's involvement in the study (start date and intervention). The purpose of this was to relax the participant and provide focus.

Each participant was then asked a series of questions (Table 9.1), however they were not necessarily asked in the same order as detailed in the Table, as is common practice in semi-structured interview methods (Whiting 2008). Further questions were asked if clarification was required or if probing was necessary to gain more details.

Table 9.1 Interview schedule/ topic guide.

Topic	Questions and prompts
Overview of experience.	Can you give me an overview of your experience of the study?  Prompts: can you describe your experience, what was your lasting memory or overall impression of doing the exercises and taking the supplements, your shoulder pain?
Aspects of exercise programme most/least enjoyed.	Were there any aspects of the exercise programme which most/ least enjoyed? What were they?
Aspects of taking supplements most/least enjoyed.	Were there any aspects of taking the supplements which you most/ least enjoyed? What were they?
Aspects of the exercise programme easiest/hardest to implement.	Were there any aspects of the exercise programme which you found easiest/ hardest to implement? What were they?
Aspects of taking the supplements easiest/hardest to implement.	Were there any aspects of taking the supplements which you found easiest/ hardest to implement?
Aspects the exercise programme, if any, continued beyond the study.	Were there any aspects the exercise programme, if any, continued beyond the study? If so which ones and to what extent? Any reasons why you continued? Any perceived benefits? Do you plan to continue long term?
Aspects of the supplement use, if any, continued beyond the study.	Were there any aspects of the supplement use, if any, continued beyond the study? If so which ones and to what extent? Any reasons why you continued? Any perceived benefits or side effects? Do you plan to continue long term?

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Factors or strategies which participants found helped them to take the supplements (Enablers).

Did you have any or find any factors or strategies which you found helped you to take the supplements (enablers)? If so what and how did they help you?

Prompts: Support from family or friends, individual skills such as organising and planning, written advice, email/phone support? Provision of supplements and the way in which they were provided?

Factors or strategies which participants found helped them to complete the exercises (Enablers).

Did you have any or find any factors or strategies which you found helped you to complete the exercises (enablers)? If so what and how did they help you?

Prompts: Support from family or friends, individual skills such as organising and planning, motivation? Provision of exercise booklet, theraband, having attended the exercise class and email/phone support?

Factors or problems which participants encountered which prevented or limited their ability to take the supplements (Barriers).

Were there any factors or problems which you encountered which prevented or limited your ability to take the supplements (barriers)? If so what, is there anything which could be done to alleviate them?

Factors or problems which participants encountered which prevented or limited their ability to carry out the exercise programme (barriers).

Were there any factors or problems which you encountered which prevented or limited your ability to carry out the exercise programme (barriers)? If so what, is there anything which could be done to alleviate them?

Physical experiences during the intervention (for example feelings of wellbeing, altered bowel habits).

Can you discuss any physical experiences during the intervention (for example feelings of wellbeing, altered bowel habits)? If yes how did these affect you? Any side effects?

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Emotional experiences during the intervention (for example feelings of control/ lack of control).	Can you discuss any emotional experiences during the intervention (for example feelings of control/ lack of control)? Do you remember any feelings or emotions during the study? If yes what were they, when did they occur? Prompts: feeling more or less in control of their condition and its treatment- ask for reasons why. Feeling more of less certain of a positive outcome from treatment?
Social consequences of the intervention and taking part in a study.	Did you find any social consequences of taking part in the study or doing the exercises/ taking the supplements? If yes how did you manage these?

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### **9.1.9 Data analysis**

A thematic style of analysis was used to explore across the data set to identify repeating patterns of meaning. This is the most common style of analysis of qualitative data and through its theoretical flexibility and freedom it can provide a rich and detailed interpretation of the data (Braun and Clarke 2006). An inductive approach was taken where there were no pre-determined themes set to explore and the analysis was data driven. The thematic analysis was undertaken using the six point guide described by (Braun and Clarke 2006). The six stages included; familiarisation with the data through reading and re-reading; the generation of initial codes using Nvivo V10 software (QSR International (UK) Ltd, London UK); then analysing and grouping the codes to generate themes, review, discussion and consensus between the researchers regarding the themes, their name and definition. Extracts from the interviews were chosen to illustrate effectively the themes and sub themes. A conceptual diagram was constructed to demonstrate the relationships between the themes and sub themes. The final stage was writing of the discussion presented in this chapter where relevant literature was reviewed and cross comparisons made with the findings of this study to enable synthesis for the reader.

Triangulation was achieved through checking of the transcripts against the original recordings and the discussions between the researchers regarding codes, themes and analysis.

## **Findings and results**

### **9.1.10 Sample description**

Twelve participants were interviewed for this study. The characteristics of the participant group are detailed in Table 9.2. There were an equal number of males and females and an equal number allocated to the treatment and placebo groups. This was determined after the group allocation codes were opened. The majority were aged between 50-69 years (50%) and employed (58%). The mean change (improvement) in the OSS over the 12 month period was 14.17 (range 0-22), with 6 points change representing a clinically meaningful change (van Kampen, Willems et al. 2013). The mean percentage change in pain intensity as measured by the numerical was 81% decrease which equates to a substantial improvement (Dworkin, Turk et al. 2008). The characteristics are representative of the participant group of the randomised controlled trial (The efficacy of polyunsaturated fatty acids and exercise in the treatment of RC tendinopathy ISRCTN 17856844) and reflect the purposeful sampling method used.

Table 9.2 Participant demographics

Variable	Interview participants (n=12)	RCT participants (n=73)
Gender: male	6 (50%)	37 (%)
Age (years)	54.83 (18.24)	52.14 (14.06)
Allocated to treatment group	6 (50%)	38 (52.1%)
Oxford shoulder score at baseline	35.67 (6.15)	31.88 (8.06)
Oxford shoulder score at 1 year	45.83 (3.27)	43.05 (6.22)
Numerical rating score at baseline	5.33 (2.75)	6.12 (1.99)
Numerical rating score at 1 year	0.92 (1.49)	2.14 (2.44)
% change in numerical rating score	81% (31.55)	65% (35.82)
Post intervention EPA & DHA plasma levels (% of fatty acids)	6.06 (4.03)	1.51 (0.50)
Supplements taken (from returned pill count)	482.91 (142.41)	446.62 (125.22)
n of exercise classes attended	6.8 (2.48)	6.04 (2.44)

Legend; n=number. Summary measures represent means (SD/ %).

### Thematic analysis and discussion

This study provides an invaluable insight into the individual participant's experiences through the trial and helps guide and shape future studies and current practice. The context of RC tendinopathy must be considered when discussing participant's experiences and their adherence to treatment in particular. The context of a condition is known to be an important influence on how a patient absorbs information and decides to use that information (Scott, Estabrooks et al. 2008). Patients with chronic conditions have been found to be less compliant, although not statistically significant, than those with acute post-operative conditions (Sluijs, Kok et al. 1993). RC tendinopathy is considered a medium term condition, with symptoms which usually resolve to some extent with treatment over a period of six to nine months and therefore the expectations of those with RC disease might be expected to be

different than those with a lifelong condition such as rheumatoid arthritis. It is well recognised that the motivation to adhere with treatment can differ depending on the condition and population (Shaw, Williams et al.).

Four main themes were identified from the analysis of the transcripts:

1. Experiences relating to participation in a scientific study
2. Self-efficacy
3. Enablers/facilitators and barriers to exercise
4. Enablers/facilitators and barriers to taking supplements

Within each theme there were sub themes reflecting the breadth of information and answers given in the interviews (Table 9.3). The sub-themes were often interlinked across themes.

Table 9.3 Themes and sub themes developed from interview transcripts

Theme A: Experience of participation in a scientific study
I) Reasons for consenting into trial; perceived personal benefit, altruism, interest in nutritional supplements
II) Experience of being a study participant, including patient-study team relationships.
III) Perceived personal benefit from being in the trial
IV) Adherence due to obligation
V) Importance of feedback and on-going monitoring
Theme B: Self efficacy
I) Education
II) Self-efficacy and coping
Theme C: Enablers/facilitators and barriers to exercise
I) Perceived benefit
II) Perceived seriousness of the condition
III) Motivation
IV) Self-discipline
V) Barriers: time, pain (both increase and decrease), equipment
VI) Equipment

- 
- VII) Strategies
  - VIII) Classes
  - IX) Patient therapist relationship
- 

#### Theme D: Enablers/facilitators and barriers to taking supplements

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- I) Enablers: ease of taking the supplements
  - II) Perceived benefit
  - III) Side effects
  - IV) Barriers
  - V) Strategies
  - VI) Ongoing supplementation
- 

#### 9.1.11 Theme A: Experience of participation in a scientific study

It was unsurprising that the first theme related to the participation in a scientific study due to the opening question asking participants to give an overview of their experience in the trial. It was broken down into five sub-themes;

- I) Their reasons for consenting into trial including perceived personal benefit, altruism and interest in nutritional supplements
- II) Their experience of being a study participant, including patient-study team relationships.
- III) Their perceived personal benefit from being in the trial
- IV) Adherence due to obligation
- V) The importance of feedback and on-going monitoring.

##### 9.1.11.1 Reasons for consenting into the trial:

Participants explained that they had been motivated to take part in the trial, in part because they had a desire to help others and for the general good.

*“I felt that the study would benefit myself plus other people.”* Participant 57.

However this willingness to help others or altruism was not their only motivator to take part and was often cited as a secondary motivator with considerations of personal benefit emerging as a key motivating factor for trial participation. This is often known as ‘conditional



altruism' (McCann, Campbell et al. 2010), where participants are happy to help others but need to see that they too will benefit from the participation in the study personally. In this nature some participants described it almost as a win-win situation where they felt they could receive personal benefit whilst helping others. These findings of conditional altruism within this study are in concordance with other studies with the primary motivating factor being perceptions of perceived benefit to them personally (Lawton, Fox et al. 2003, Garcea, Lloyd et al. 2005, McCann, Campbell et al. 2010, Locock and Smith 2011, Irani and Richmond 2015).

Participants were motivated to take part in the study by both the trial processes (specialist assessments and additional symptom monitoring and assistance as part of the trial follow up which they were aware was over and above routine treatment) and by the interventions (the PUFA or placebo supplements which was over and above routine treatment) which were perceived as sources of potential benefit.

Some participants were clearly interested in the concept of nutritional supplements being used to 'treat' their shoulder pain and this curiosity was part of their motivation to participate;

*"I just wanted my shoulder to get better and I thought it would be interesting to find out if the fish oils helped. I hadn't thought of taking a nutritional supplement."* Participant 60.

There is much publicity in the media regarding nutritional supplements and fish oils or omega 3s in particular (Greiner, Clegg Smith et al. 2010). There are frequent news articles highlighting their benefit for a wide range of conditions and it's likely that that this widespread exposure to these positive messages might influence the wider population and their interest in the use of nutrition (Rahmawaty, Charlton et al. 2013).

#### **9.1.11.2 Experience of being a study participant:**

The majority of the participants reported they found the overall experience of taking part in the trial enjoyable and interesting with one presenting a more ambivalent view;

*"I enjoyed it and found it interesting."* Participant 64.

*"Very positive."* Participant 60.

*"Very good overall experience."* Participant 57.

Although one participant was not so emphatic with his response regarding his experience in the trial,

*“I didn’t suffer from it and I can’t say I actually benefitted from it.”* Participant 74.

As part of their experience in the study, participants discussed their relationship with the study team and the participants emphasised the importance of the clinical relationship that the participant has with the research team.

*“It was so nice to come, I never wanted to miss it....it was a treat. I think that’s an important thing to remember.”* Participant 60.

*“It was certainly a pleasant way to spend some time.”* Participant 76.

The context of these comments must be considered in that the participant was telling the interviewer who had also delivered the study intervention. Therefore there is an inherent bias which must be acknowledged.

Another aspect of the trial participation which participants commented on was the feeling of obligation to the trial or the scientific process of the trial which increased their motivation or ability to adhere with the prescribed treatments.

*“Because I knew I was in the programme I took them.”* Participant 56.

*“The study gave me the incentive to carry on doing the exercises and so I was quite pleased with that and also to have a measure made of how well I was progressing.”* Participant 62.

This comment raises the theme of the importance of monitoring or follow up to support successful engagement with the treatment protocol but also was cited as one of the benefits of participating in the trial.

#### **9.1.11.3 Perceived personal benefit gained from participation in the trial:**

The majority of participants reported they felt they benefited from the treatment provided and their involvement within the trial.

*"I was relieved of all that misery and torture by joining the study so it has been extremely helpful to me, extremely."* Participant 70.

*"It has been good because I felt that physio didn't achieve as much as I had hoped it would. The study gave me the incentive to carry on doing the exercises and so I was quite pleased with that and also to have a measure made of how well I was progressing."* Participant 62.

Feedback was highlighted as a key benefit which some participants reported gave them motivation to continue.

*"Because I received regular feedback, so I was motivated to carry on."* Participant 60.

The additional monitoring and supervision that the participants received as part of the trial with was additional to routine treatment was also cited as a positive benefit of participation.

*"It was really good to have those follow ups and ask questions and to modify exercises. I found that really useful.....to actually be able to speak to a physio and get a second opinion about my progress and to alleviate any worries that I had as well, so I found that very useful and it was good that you had that consistently."* Participant 75.

*"Follow up at six months or a year is really helpful as you can use it as a marker to see where you are."* Participant 57.

*"I was pleased the study was going on longer than that [shoulder class] so it gave me a programme to work to...but more monitoring would do it you know. This is what I feel I had being part of the study but which I didn't get as part of routine treatment."* Participant 62.

*"I would have stopped doing it [the exercises] then [on discharge from the class at eight weeks] so the further follow up was very useful to me."* Participant 60.

One participant voiced his concerns about being discharged from the shoulder class.

*"They were quite happy to discharge me without seeing me first, it was a bit disheartening.....whether I would have gone as far as going to my GP to get a further referral I*

*just don't know...I might have. Or I might have tried the osteopath again, although that hadn't been successful."* Participant 62.

Others felt that they were recovering well on discharge from the class and would *have* been happy to cease treatment at that point with no further desire to have been followed up or monitored;

*"The assessments, I wouldn't honestly say I found them helpful because the condition was clearing up....I would have been happy to leave physio at 8 weeks."* Participant 76.

The expressed preference of the majority of participants for the ongoing support and follow up is in concordance with studies investigating barriers and enablers to adherence with a home exercise programme for RC tendinopathy (Sluijs, Kok et al. 1993, Locock and Smith 2011, Littlewood, Malliaras et al. 2014). The feedback and monitoring is essential in conveying the importance and value of the rehabilitative process, progressing exercises where appropriate in order to gain maximal outcome as well as recognising the patient's efforts, their progress and achievements. Patients may be motivated by a desire to please or not let down healthcare professionals (Riolo 1993, Littlewood, Malliaras et al. 2014).

#### **9.1.12 Theme B: Self-Efficacy**

Self-efficacy in terms of healthcare was first defined by as,

*"The belief in one's capabilities to organise and execute the course of action required to produce given attainments"* (Bandura 1977) p3.

The degree of an individual's self-efficacy is important in the rehabilitation process as it can influence the engagement of the individual in the rehabilitation and the extent to which they will persevere when faced with difficulties or distractions (Barlow 2010) and can determine how they incorporate a treatment plan or exercise programme into their everyday lives (Littlewood, Malliaras et al. 2014).

The importance placed on being able to manage their own condition through improved knowledge and a feeling of increased control was highlighted as a theme within the participants' transcripts.

*"I was very down in the dumps because I was constantly in discomfort and no-one was listening and once I'd started the exercises and whatever I was taking I found it was a lot easier because I felt it was something I could manage myself and I could control what I was doing."* Participant 57.

*"I've been through a series of classes and I've seen the benefits. I've just come to the realisation that it is something that I just have to manage and by doing the exercises I feel I can manage it...exercise is key for me."* Participant 75.

Part of achieving self-management and self-efficacy is through providing the participants with greater knowledge and education about their condition.

*"It [the trial] changed the way I was thinking about the shoulder and I find exercises that help .....They explain regarding your shoulder or chronic pain so you have more control what to do or what not to do, and things that can improve your situation. That was also good."* Participant 56.

Despite the education sessions within the classes, the contact with physiotherapists and participation in the study with contact with the study team two participants expressed that they still did not really know what had been wrong with their shoulder and if he had been asked to describe it one said he would say;

*"Well my shoulder hurt and after a while it stopped hurting."* Participant 76.

*"I still am [vague] about what was actually wrong. Other than the fact it is clearly something that has been around for a long while and flared up but I don't really know why it should have suddenly gone or why it's taken so long to get right."* Participant 62.

Education regarding the condition, the treatment options available and the expected recovery period have all been found to be key components to facilitate adherence to treatment (Ireland 2003). This is especially the case with RC tendinopathy where a meaningful recovery often takes several months (Bennell, Wee et al. 2010). Indeed one participant commented;

*“At first I expected to see an improvement within a few weeks but it was so small. They tried to encourage me saying it was a long haul and by the end they said it would be six to nine months. I think it might have helped to know the six to nine month time frame at the beginning.”* Participant 62.

This illustrates and emphasises the need to find strategies to educate patients regarding expected rehabilitation and recovery times in order to ensure their expectations are realistic.

#### **9.1.12.1 Enablers/facilitators/motivators and barriers to exercise**

Enablers and barriers are to be discussed the same section as for some factors such as pain, it was found to interestingly be a barrier for some and a facilitator for others.

##### **9.1.12.1.1 Enablers – Exercise class**

The exercise group was cited as being good fun and helpful by several participants;

*“The group aspect was good, it was really fun.....I enjoyed doing the exercises every Thursday morning, it was one hours really fun and that really helped me a lot.”* Participant 56.

Group exercise has been found to be beneficial in other physiotherapy studies where peer support has been cited as a benefit of class based exercise over individual exercise (Lewis, Hewitt et al. 2005, Kaapa, Frantsi et al. 2006).

The enjoyment of the exercise class coupled with the supervision and assistance given to them within the class proved to be an enabler to them exercising.

*“I think I found it helpful to ahhh have the class to go to because it meant that I was doing the exercises better.”* Participant 66.

The schedule provided by coming to a weekly class also served as an enabler or motivator for a couple of participants;

*“Having a schedule coming up here provided a bit of an incentive.”* Participant 62.

*"I'm not very good at doing exercise...I get bored very easily so that type of thing [exercise class] is good for me."* Participant 66.

The expectation that they were there to exercise was also expressed to be an enabler, *"The classes were easy because it was an environment where it was expected that there were things to be done."* Participant 62.

The valued placed on the knowledge and expertise of the physiotherapists running the class was highlighted as another key area.

*"It was great there was a dedicated physiotherapy team."* Participant 75.

One participant made a comment regarding the number of physios or assistants supervising in the class;

*"Continuity of physios in the class would have helped as I had to keep reminding them of what I was doing.....Fewer physios were better than lots as then they knew what was going on."* Participant 57.

This raises an important point in that quantity of staff in a class setting does not always improve the level of care. Thus implying there is a critical mass or level of staffing where disadvantages outweigh the benefits.

#### **9.1.12.1.2 Enabler- self-discipline**

Self-discipline was mentioned as a key enabler for one participant, this was coupled with their strong internal locus of control;

*"I was very strict with myself about doing the home exercises."* Participant 57.

Locus of control is known to be a factor when considering adherence and those with an internally orientated locus of control is believed to be more likely to be health conscious and to be adherent with treatment programmes (Groth and Wulf 1995).

#### 9.1.12.1.3 Enabler- pain

Pain was found to have been a motivator, enabler and facilitator to exercise. In some, exercise decreased their shoulder pain and therefore this increased their motivation and incentive to continue with the exercises and get continued and or increased relief. Initially it is often the pain at its peak which has led the person to seek treatment and thus it served as a prompt or reminder to do the exercises.

*“As I was getting better, my motivation increased.”* Participant 60.

This concept also links into perceived benefit from the treatment where if the treatment works then the patient is believed to be more likely to continue with it. Littlewood et al (2014) found that quick and meaningful relief in pain or response to therapy was a crucial feature of continued adherence to treatment.

Pain was also used to assist in the self-management of the condition. Participants described re-starting the exercises when they experienced pain again.

*“My arm does start aching and I go straight back into exercise mode and it relieves the condition.”* Participant 57.

By finding something that they could do to alleviate the pain when it returned supported development of their control and self-management;

*“Pain is reminding me usually to do it [the exercise programme].”* Participant 75.

In this case pain served as the prompt to remind the participant to carry out her exercises.

#### 9.1.12.1.4 Enabler- perceived benefit of treatment

As mentioned previously the perception that the treatment they were undergoing appeared to have helped some to continue adhering to the exercise prescribed;

*“I knew if I didn’t do it [the home exercise programme] it wouldn’t improve and strangely enough I do get occasions where my arm does start aching and I go straight back into exercise mode and it relieves the condition.”* Participant 57.



*“It’s easier to do the exercises when you can feel a definite benefit. It’s always hard to exercise to prevent something from getting worse.”* Participant 66.

Similar themes emerged from a study investigating non-adherence with exercise programmes in patients with cystic fibrosis (Abbott, Dodd et al. 1994). The authors commented that the patients in their study appeared to use their symptoms as an indicator to continue or stop the treatment, thereby focusing on the short-term benefits or disadvantages of treatment as compared with the long-term benefits. Adherence improved when immediate benefits could be seen by the patient, supporting the belief that patients who believe in their treatment are more likely to comply. This is interlinked with the relationship between the perceived balance between the costs and benefits of rehabilitation (Groth and Wulf 1995).

Participants also acknowledged the possible role that natural resolution might have made in their improvement;

*“My improvement must be due to the exercises although I don’t know how much I would have improved with no treatment at all.”* Participant 62.

*“It was getting better but whether it was getting better due to treatment or just natural progression of things improving themselves with exercise and all I can’t really say.”* Participant 74.

#### **9.1.12.1.5 Enabler equipment**

Several participants reported the Theraband <sup>™</sup> (Performance Health, Akron, Ohio, USA) which was provided to the participants to allow them to carry out the home exercise programme, as a key enabler. They found the resistance exercises were effective and found it a reminder or visual prompt to do them;

*“Working with the band is probably a good idea because you can do it everywhere and anywhere.”* Participant 64.

*“The elastic band, I think, is worth the money and I liked being able to go up the levels....I felt like I was progressing.”* Participant 60.

The use of the gym equipment proved to be an enabler for the class;

*"Lots of equipment in the room and most I couldn't have at home or replicate the gym at home so it [the class] was really useful."* Participant 75.

#### **9.1.12.1.6 Enabler- participation within the study and the further follow up**

The follow up period to one year was cited by some participants as giving the motivation to continue to do the exercises;

*"The study gave me the incentive to carry on doing the exercises."* Participant 62.

#### **9.1.12.1.7 Barriers to exercise within the trial:**

There were several barriers cited by the participants preventing them from either fully or partially adhering to the exercise regimen including time, memory, the exercise class, equipment, self-discipline, pain, perceived seriousness of the condition and participants cited both time and memory as reasons for not being able to do the exercises as prescribed;

*"Never find time."* Participant 56 and *"Failing memory made me forget occasionally."* Participant 69.

Time and the need to fit in an extra thing during the day have been frequently cited in the literature as barriers to exercise (Sluijs, Kok et al. 1993, Littlewood, Malliaras et al. 2014).

#### **9.1.12.1.8 Barrier- timing, frequency and location of class**

Timing and distance to class were both cited as barriers to attending

*"I was working so it was difficult with the timing."* Participant 60.

*"Distance to the class was too much of a barrier."* Participant 69.

In terms of frequency there were differing views. For some once a week was perfect;

*"Once a week was enough because it could then be fitted into your work schedule."* Participant 57.

Another said *"I wish you could have a class every day."* Participant 56.

The actual number of classes offered was also a subject of discordance with one participant being *“pretty unhappy”* Participant 62 at discharge, and others reporting *“the proof is in the pudding that there were enough classes and I don’t have a problem now.”* Participant 64.

#### 9.1.12.1.9 **Barrier equipment:**

Whilst the Theraband <sup>™</sup> and gym equipment were enablers for some the lack of equipment was found to be a barrier for home exercise as participants felt they did not have the necessary equipment;

*“At home it was difficult to do the exercises due to the lack of equipment.”* Participant 60.

This theme was repeated by several other participants;

*“They [the home exercises] were quite hard. I know this is silly but it was quite hard in a way to do them at home. They are quite awkward things and you don’t have the right kind of equipment as you have in the gym.....It was a bit awkward to find a suitable place.”* Participant 76.

#### 9.1.12.1.10 **Barrier- self-discipline and lack of motivation**

Some participants expressed it was their lack of motivation and self-discipline which was the overwhelming barrier to exercise;

*“At home there was the problem with self-discipline, finding the time for it. But I have got loads of time but still its self-discipline that’s always the problem.....the big problem was lack of motivation.”* Participant 62.

It is unsurprising that this was expressed in the data within this study as low self-efficacy, depression, anxiety, helplessness and poor self-discipline have all been found to be barriers to treatment adherence (Jack, McLean et al. 2010).

#### 9.1.12.1.11 **Barrier pain:**

Pain has been found in the literature to be a barrier to exercise, especially worsening pain with exercise (Minor and Brown 1993, Jack, McLean et al. 2010). Pain both increasing and reducing levels of pain were found to function as a barrier. In some participants as their pain decreased and shoulder function increased the motivation to do the exercises decreased as there seemed less of a need for them;

*“Those exercises were hurting me and I was not benefitting at all.”* Participant 70.

*“There was one exercise that I was given earlier that I thought at the time might have made things worse, so I stopped doing it”* participant 69.

A common theme amongst a proportion of the participants was that pain acted as a prompt to remind the patients to do the exercises when they experienced their shoulder pain. It stands to reason that these were also the participants who reported reduced adherence to exercise as their pain diminished and with it the reminder to do their exercises;

*“As with everything, as progress is made its harder to get the incentive to keep up with the exercises.”* Participant 62.

Here motivation is also the barrier as their improvement continues their motivation drops;

*“I didn’t continue with them because the shoulder seemed to be improving and there didn’t seem to be a need for them.”* Participant 74.

The relationship between the reduction in the impact that the condition is having on the person’s life and the reduction in the adherence is intrinsically interlinked. As the illness becomes less important in the person’s life and the perceived seriousness of it reduces. Sluijjs et al (1993) who investigated physiotherapist’s and patient’s beliefs regarding adherence with exercises in the private sector in the Netherlands found that the degree of disability provided the strongest link with the level of adherence with an exercise programme. Those whose condition caused greater difficulties with functioning demonstrated greater adherence to the home exercise programme than those who had less hindrance from their condition;

*"I think the low level of my condition meant I was not highly motivated [to do the exercises]."*

Participant 76.

#### 9.1.12.1.12 Barrier -Efficacy of exercises:

As mentioned in the enablers to exercise section the perceived effectiveness of the exercises the participants had been given was a key factor in whether they continued with them or not;

*"I was not benefiting from those exercises at all."* Participant 70.

The individualisation of treatment in a class setting is a challenge and some class attendees run the risk of feeling that they are being given a one size fits all approach as one participant voiced in the interview;

*"There were several people in the group, everybody doing the same exercise and I did those exercises. I had several sessions but it didn't help at all."* Participant 70.

#### 9.1.12.1.13 Barriers- expectations

Expectations of both the clinicians and the participants were raised as themes within the interviews. Expectation is a complex theme as it encompasses a patient's expectations that the treatment will ultimately improve their condition. In addition, it includes, expectations of what the treatment involves and their role to play in treatment. As well as, the physiotherapists' expectations of the improvement a patient should have made at discharge and the expectations of the participants in the exercise class of their fellow exercisers;

*"I think some of the people there were just going through the motions. But I wasn't because I wanted to get it right. So I was a bit unhappy about that."* Participant 62.

The physiotherapy team were felt to have "low expectations" according to some participants at discharge and one reported;

*"They were quite prepared to discharge me without seeing me first, it was a bit disheartening."*

Participant 62.

Others reported;

*"I was 60% better and so there was still something there.....probably I would have been able to at least carry on [with the exercises] until I felt that it was good enough."* Participant 66.

#### **9.1.12.1.14 Strategies to help with adherence and motivation to exercise**

Interviewees described particular strategies which they adopted and found to be beneficial in helping them adhere to the exercise programme. These all centred on building the exercises into their everyday well established routine;

*"I always did the exercises when I had my shower in the morning and got dressed and went into exercise mode. I did it without fail so it was easier when I linked it to an activity."*

Participant 57.

*"Band is tied to the handle of my office door so I can't get out without doing them."* Participant 78.

Or whilst doing something else which served as a distraction;

*"I tried to do it when there was something on the radio that I could do at the same time"*

Participant 69.

Other studies have found that those who integrated their exercise programme into their lifestyle managed a great level of adherence with minimal behavioural change (Williams and Adams 2000).

#### **9.1.12.2 Enablers/ facilitators/ motivators and barriers to taking supplements**

Adherence to medication is known to be inconsistent with 30-50% of medications not being taken as recommended, irrespective of the seriousness of the condition for which the medication is being taken (Haynes, McKibbin et al. 1996, DiMatteo 2004). One participant within this study ceased taking the supplements after two weeks due to difficulty taking them; the others reported to being fundamentally adherent to taking the supplements as recorded in the diaries and when the returned capsule count was assessed.

One participant voiced their difficulty in swallowing the supplements due to their physical size and quantity;

*"I found them [the capsules] quite difficult to take. I am not the best with tablets anyway but they were really big so swallowing was an issue and the taste."* Participant 75.

Others had no problems and found them;

*"Quite easy to take."* Participant 64.

*"They are quite big tablets and there are three of them, so you are certainly very conscious that you are taking lots of tablets."* Participant 66.

Whilst this on the surface might be considered a barrier it could also be considered as a motivator due to the fact that by being cognizant of taking tablets you are doing something for the condition as highlighted by the comment;

*"The tablets made me feel much better but I don't know how far that is if you take lots of tablets you must feel much better."* Participant 66.

Others also reported that whilst they were taking the nine capsules a day they had no problems in remembering to take them but once the dose was stopped and they returned to one a day or their usual intake they had difficulty in remembering;

*"Oddly enough it was really easy to take the nine a day. As soon as I was only taking one or two I kept forgetting them. So I was very good as long as I was taking nine."* Participant 60.

*"Just the fact you are taking nine a day you tend not to forget about it too easily."* Participant 74.

#### 9.1.12.2.1 Perceived benefit:

The participants' perception of the beneficial effect of the supplements emerged as a theme but interestingly a lack of perceived benefit did not appear to affect adherence unlike with the home exercise programme;

*"I suppose the benefits weren't really very obvious. I understood what they were for but there wasn't an immediate pay off."* Participant 76.

This is possibly due to the fact that the participants were aware they were enrolled in the study;

*"Because I knew I was in the programme and I have to take them."* Participant 56.

Other participants had differing perceptions of the benefits afforded by the supplements they were taking;

*"I felt a little more energetic after taking those pills."* Participant 70.

*"I felt a real difference taking the supplements.....very quickly notice a benefit in being able to move more freely. I am not sure if this was due to the exercises or supplements."* Participant 57.

*"I think they've made me stronger. I feel I do have lots of skin problems always and I felt it helped with those as well."* Participant 60.

*"The tablets made me feel much better....I occasionally get aching knees and aching back and I was kind of telling myself, ohhh I feel they are much better too so, I remember having the feeling that they felt better whilst taking the tablets but again I couldn't really be sure whether it was."* Participant 66.

#### 9.1.12.2.2 Enablers

Being used to taking daily medication served as a routine to help remind to take the capsules;



*"I already had a good pill routine established morning and night it was a scheduled thing and that's easy to remember."* Participant 62.

Several participants cited taking the supplements with meals as part of a well-established routine helped prompt them or remind them to take them. This may have been due to the suggested capsule administration instructions given to each participant.

*"Linking to meals reminded me to take them. I put them out in the morning and carried them around with me."* Participant 57.

The pots of pills served as a visual reminder or prompt to take the supplements with participants reporting they kept them in the by their bed, in the kitchen or by their coffee or kettle in order to prompt them to take them;

*"Wherever I go I just carry one pot with me so that would remind me."* Participant 56.

*"Two big containers of pills were a reminder in themselves."* Participant 74.

#### **9.1.12.2.3 Barriers:**

Some participants reported forgetting to take the supplements;

*"It is hard to take 9 a day. It's not hard physically it's just hard to remember to take them."* Participant 78.

#### **9.1.12.3 Side effects:**

The interviewees were asked if they had noticed any side effects whilst taking the pills. Two responded by saying they had had side effects;

*"Bowel movements seemed to be a bit more solid than usual."* Participant 74.

*"I think some of the supplements gave me a dodgy tummy but I can't be sure whether it was that or something else. I wouldn't be convinced that they did."* Participant 78.

One participant did raise the question of if there are any health side effects of taking the fish oils and the amount of mercury that can be in oily fish. However, this had not affected his decision to adhere with the treatment.

#### 9.1.12.4 Strategies to help with adherence and motivation to taking the supplements

Participants suggested ways in which their adherence could have been enhanced within the trial but these are also potential strategies which might enhance adherence in clinical practice;

*“The fact you had to take them in the day as well when you are working it just wasn’t practical for me, so maybe stronger dose and smaller capsules.”* Participant 75.

*“Mechanisms, calendar appointments that would be relatively easy to set up on phones.”* Participant 76.

*“A daily notification or even an email from yourselves you know it would be really helpful.”* Participant 76.

## Discussion

The themes and sub-themes expressed within this study are pertinent to clinical practice and inform clinicians regarding the barriers and facilitators to adherence. Barriers and enablers to exercise indicate that there are few key areas which could be enhanced in order to maximise patient’s engagement with their treatment.

With regards to exercise, the participants reported they valued the follow up and more intensive monitoring and feedback regarding their progress and condition which they received on the trial. This increased monitoring has also been shown to statistically improve outcomes in a study investigating the effects of monitoring on outcome for a group of patients undergoing exercise therapy for lower back pain. The experimental group (n=20) undertook a supervised and monitored pre designed exercise programme, where each session was monitored by a certified strength and conditioning specialist within a health club, compared to the control group (n=20) who were given the pre designed exercises and advised to exercise four times within a health club a week for six months. Statistically significant increases in strength and aerobic fitness along ( $p=0.01$ ) with decreases in pain ( $p=0.01$ ) and body fat ( $p=0.05$ ) were observed in the experimental group. The mean number of exercise sessions

completed (90.8 out of 96 in the experimental group compared to 31.9 in the control) was also statistically significant ( $p=0.01$ ) indicating that the supervision and monitoring had a profound effect of adherence within this cohort of patients. It is unrealistic to imagine that this level of supervision would be possible in current clinical practice within the NHS. However it might be possible to schedule an additional review appointment a few months after the time the patient is discharged. This might further encourage and motivate the individual to continue with the exercise programme and may (if future research demonstrates) translate to improved outcomes.

This additional review appointment could potentially take the form of; face to face appointments, a telephone call, or email correspondence depending on resource availability and patient preference. This review appointment could also serve to progress their exercises if required, so that they were more relevant to that patient at that time. This links with another enabler that was highlighted within the current study; being the importance of the perceived benefit of treatment. This further emphasises the need for the right exercises or treatment plan for that individual so that they can see that progress is being made. Accurate information must be given to the patient at the beginning of treatment informing them of the expected timescales involved. The participants responses also suggest that the right equipment should be provided and possibly a suggestion or collaborative approach to working out how this might be incorporated into their day or routine.

It might be beneficial in a class setting to allow patients to manage their own attendance and discharge. This study highlighted that some participants felt they had attended enough or too many classes and others would have preferred more. One suggestion might be that patients could elect when to leave the class and continue with exercises at home. Thus reducing non-attendance and allowing those who need more classes to access these within reason.

In terms of enablers and barriers to supplement use, the participants in this study highlighted that the size, taste and number of capsules they were asked to take were in some cases problematic. The MaxEPA capsules used in this study were chosen for specific reasons detailed in Chapter 8.2.7 including the availability of a matched placebo. However nutritional supplement manufacturers do produce and sell 'maximum strength' and 'high strength' capsules which would mean that, in order to achieve a similar dose as the 2.6g Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) given in the RCT, patients would

instead need to take four to five capsules rather than nine a day. This may lead to better adherence and could be taken with breakfast and evening meals. However, some participants raised the point that it was easier to remember to take them when there were so many.

Participants cited forgetfulness as a barrier and suggestions were made regarding smart phone reminders or daily emails from the research team in order to aid memory. M-health or mobile-health is a term which is used to describe the support of health care and public health through the use of mobile devices (Free, Phillips et al. 2013). A systematic review investigating the effect of m-health on chronic disease concluded there was mixed evidence supporting its use (Hamine, Gerth-Guyette et al. 2015). The potential for benefit is clear with the widespread use of mobile and wireless devices throughout the world but currently evidence to support its influence on adherence is inconclusive.

The importance of linking taking supplements with an already established routine was highlighted within the transcripts. The established routines were either pill taking routines and the supplements were simply viewed as another medication. Or functional routines such as washing, dressing or meal times, where the taking of the supplements were incorporated as part of that daily routine. These strategies could be suggested and discussed with patients to collaboratively problem solve in order to maximise adherence in a clinical setting.

The media coverage of nutritional supplements is patchy at best and often of questionable quality (Bartlett, Sterne et al. 2002, Robinson, Coutinho et al. 2013). One participant was interested in the study and keen to learn more about PUFAs in part due to positive media coverage. Another raised concerns regarding the possibility of mercury accumulation from taking fish oils. This was in direct response to a news article that the participant had read. The influence the media has on health perceptions is substantial and the importance of appropriately balanced and accurate reporting in the press cannot be overemphasised.

#### **9.1.13 Strengths and limitations**

The sample size was small within this study and participants were selected pragmatically due to the resources available.

The concept of this qualitative study was conceived and developed during recruitment for the main RCT and as such the resources were limited as the majority of resources were already

committed. Thus, whilst it was the aim of this study that theoretical saturation would be reached it is unlikely to have occurred.

A grounded theory approach was used in this study to influence subsequent interviews after analysis of preceding data. Whilst this allows rich and detailed data collection to occur over time and at many different levels it also carries with it the risk of researcher bias with preconceived assumptions and the potential narrowing of the topic field. In order to try to mitigate this the researcher's ideas and thoughts during and before the process were documented. This heightened her awareness to her preconceptions and how this might interact with the data. Each interview was conducted starting with broad opening questions to allow the participant to steer the conversation and provide the information they felt was relevant.

The interviewer was the physiotherapist whom had assessed the participants, delivered the intervention and designed the study. This carries an inherent bias. Whilst the interviewees were put at ease and invited to explore the negative as well as the positive aspects of the trial and the experiences some might have been reluctant about being honest or held back with some of their responses. However the positionality of the interviewer also brought some advantages, an in-depth understanding of the intervention and a working therapist-patient relationship having met the participants on a minimum of five occasions previously. It must also be acknowledged that although there was triangulation of the data from a supervisor who is also a physiotherapist to agree themes the interpretation of the data is largely the perspective of one physiotherapist. Another researcher examining the raw data might well have elicited different themes.

The interviews were conducted ten months after the intervention had ceased. This undoubtedly challenges the recall of the events, experiences and feelings at the time the participant was involved in the RCT.

The key strength of this study is in the additional information it provides to support the RCT, by, providing a voice for the participant's views and opinions through its qualitative methodology. It raises pertinent questions regarding the duration and nature of routine follow up for patients with RC tendinopathy within the NHS.

Additionally, the level of education attained by the participants was also not recorded in this study. This has previously been shown to be significantly related to adherence (Sluijs, Kok et al. 1993, Groth and Wulf 1995).

### **Conclusion**

This study explored the experiences of participants' taking part in the main RCT and the enablers or barriers to adherence with the exercise based intervention and the prescribed supplements.

Participants valued their experience within the study as largely being a positive one. The main enablers to exercise were highlighted as equipment, the perceived benefit from the actual exercises, and the longer follow up and more intensive monitoring and feedback received in the trial. Barriers included motivation, lack of suitable equipment and pain whether it improving or worsening. Enablers to supplement taking included, perceived benefit of the supplements and a systematic pill taking routine. Barriers were largely the size, taste and quantity of supplements to be taken, remembering to take them, and, a lack of perceived benefit.

## **Chapter 10 : Discussion**

## Introduction

Research investigations have repeatedly demonstrated that exercise is an effective treatment for people diagnosed with rotator cuff (RC) tendinopathy (Ainsworth, Lewis et al. 2009, Littlewood, Bateman et al. 2016). Exercise is as effective as surgery in the treatment of subacromial impingement syndrome (Haahr and Andersen 2006, Ketola, Lehtinen et al. 2009, Ketola, Lehtinen et al. 2013), partial thickness RC tears (Denkers, Pletsch et al. 2012) and atraumatic full thickness tears (Ainsworth 2006). However, comparable to the outcomes from surgical trials, not all patients achieve full resolution of their symptoms with a graduated exercise programme.

Inflammation is considered to be present as part of the continuum of pathology in RC tendinopathy (Dean, Franklin et al. 2012, Rees, Stride et al. 2013, Dean, Gettings et al. 2015). Non steroidal anti inflammatory drugs and cortico-steroids are commonly prescribed to treat RC tendinopathy (Buchbinder, Green et al. 2003, Arroll and Goodyear-Smith 2005, Boudreault, Desmeules et al. 2014) but these medications are associated with side effects including; nausea, dyspepsia, vomiting, abdominal pain and heartburn (Brun and Jones 2001), gastrointestinal ulceration (Rainsford 1999), and impaired tendon healing (Dean, Franklin et al. 2014) and also do not always alleviate the symptoms (Coombes, Bisset et al. 2010). Due to incomplete resolution of symptoms with current treatments, new therapies that may target the underlying patho-aetiology and may be less harmful than conventional therapies (Rainsford 1999, Brun and Jones 2001, Dean, Franklin et al. 2014) need be considered and trialled. Long-chain omega-3 polyunsaturated fatty acids (PUFA) were claimed to be effective in the treatment of a range of tendinopathies including supraspinatus, infraspinatus, long head of biceps, medial and lateral epicondylitis and patellar tendinopathy (Mavrogenis, Johannessen et al. 2004). However this study was associated with a high risk of bias because analysis was not on an intention-to-treat basis and non-compliers were excluded from the data analysis.

One reason long-chain omega-3 PUFAs may benefit people diagnosed with RC tendinopathy is because they have the potential to target inflammatory cells and processes (Calder 2006, Das 2006). Research investigating the effectiveness of long-chain omega-3 PUFAs in this condition would be of clinical relevance due to their potential role in symptom reduction with a lower risk profile than other interventions (Rainsford 1999, Brun and Jones 2001, Dean, Franklin et al. 2014).



As such, one aim of this thesis was to investigate the use of long-chain omega-3 PUFAs and exercise in the treatment of RC tendinopathy.

This hypothesis formed the main clinical investigation of this thesis. Other research was conducted to support the main clinical trial. A reliability study was conducted (Chapter 6) to determine the intra and inter-tester reliability of the impairment outcome measures used in this investigation. This work has subsequently been published (Dollings, Sandford et al. 2011).

Additional research investigated the reasons for self-prescription of dietary supplements in a cohort of people attending physiotherapy for shoulder pain. To achieve this, a cross sectional survey was conducted. An additional qualitative study explored the enablers and barriers to both exercise and supplement consumption for people diagnosed with RC tendinopathy.

This group of studies, which explores novel treatments for RC tendinopathy, is particularly pertinent in the current health care environment of 'health based practice' where maximisation of an individual's health and well-being for the long term as well as treating the presenting complaint is paramount (Dean, Al-Obaidi et al. 2011).

## **Summary of findings**

### **10.1.1 Questionnaire study:**

The survey study revealed that 38% of respondents were taking dietary supplements. Eighty-two percent of those taking supplements (n=82) reported taking supplements to address their shoulder pain. The most commonly listed supplement was cod liver oil, but this was, on average, consumed at a dose which would not be expected to have an anti-inflammatory effect. In this investigation, women were found to be taking more supplements than men, and increased supplement use was found to be associated with increasing age. Friends and family were ranked the highest in sources of influence with regards to supplement use followed by the media and internet. One key point derived from the survey study was that the uncertainty of the evidence and the perceived lack of efficacy of supplements which proved to be a barrier to use and this was also echoed in the qualitative study (Chapter 9). The concerns expressed by the respondents of the questionnaire pertaining to lack of efficacy of supplements were supported by the findings of main clinical study.

### **10.1.2 Evidence from randomized controlled trial:**

The placebo-controlled RCT described in this thesis failed to demonstrate any benefit of long-chain omega-3 PUFA supplementation on clinical outcomes in RC tendinopathy. However, there was tentative evidence to suggest a more rapid improvement in disability and pain as measured by Shoulder Pain and Disability Index (SPADI) ( $p=0.003$ ) in the long-chain omega-3 PUFA treated group at the three month time point. However, as this was not the specified primary outcome, this could be a chance finding and needs confirmation. Participants received 9g of oil daily which would be estimated to provide 2.6 g of EPA and DHA or approximately 3 g long-chain omega-3 fatty acids/d. While higher doses may theoretically have effects, the level of supplementation used is at the upper limit likely to be consumed for non-medicinal purposes.

### **10.1.3 Qualitative study;**

The qualitative study demonstrated that participants valued their participation within the RCT expressing it was largely a positive experience. The principal enablers to exercise were highlighted as; equipment, the perceived benefit of the exercises and long term follow up and supervision. Barriers to exercise included poor motivation, lack of suitable equipment and pain either worsening or improving. Enablers to supplement use were found to be; perceived benefit of the supplements and a well-established pill taking routine. Barriers to supplement use were; the large size, taste and quantity of capsules to be taken along with the lack of perceived benefit from them.

No adverse effects were reported by the participants within the study other than mild gastrointestinal upsets by two participants, both of which were in the long-chain omega-3 PUFA treatment group.

## **Strengths and Limitations**

A strength of the randomised controlled trial is in its double-blind design and the use of multiple clinical outcomes. However, the more outcomes specified, the greater the likelihood that some may be found to be significant. The primary hypothesis looked for a difference in OSS of 6 points whereas the observed difference between treatments was 0.2 points. The 6-7 point improvement in disability and pain observed in both treatment groups over the first two

months of treatment is in keeping with the results of other studies investigating the efficacy of exercise and physiotherapy in RC tendinopathy (Littlewood, Bateman et al. 2016).

At the time the RCT was being designed the primary outcome measure, the OSS, was and remains for some, the most clinically preferred shoulder outcome measure (Varghese, Lamb et al. 2014) and is still in common use in research (Carr, Rees et al. 2014). The SPADI (a secondary outcome measure used in this study) may be more responsive than the OSS (Ekeberg, Bautz-Holter et al. 2008). The test re-test reliability was found to be greater for the SPADI than the OSS in subacromial impingement with the weighted Kappa coefficients being moderate to very good for the SPADI (0.51 to 0.80) and fair to good for the OSS (0.13 to 0.78) (Cloke, Lynn et al. 2005). This could offer a further possible explanation for the significant difference in disability and pain (as measured by the SPADI) observed in favour of the long-chain omega-3 PUFA group at three months.

Another potential limitation was that there was more than one physiotherapist examining participants and this is a potential source of error. However, the reliability study demonstrated adequate inter-rater reliability of the impairment measures between the two examiners. The primary outcome and other secondary measures were self-report questionnaires and so it is thought the risk of error through this means is likely to be small.

#### **10.1.4 Natural recovery**

The course of natural improvement of RC tendinopathy is currently uncertain. Those with musculoskeletal symptoms such as RC tendinopathy often seek treatment at the peak of their symptoms and subsequent improvement is usually inevitable (Krogsboll, Hrobjartsson et al. 2009). It is also possible that the improvement in disability and pain observed in both groups was due to natural resolution. Without a control group it is impossible to quantify the effect that natural resolution had on the symptoms of the participants within the RCT in this thesis. However in other studies that have included a no treatment control group minimal improvements have been observed in pain and function (Lombardi, Magri et al. 2008).

Within this study only 35% of participants reported that they were completely pain free at one year. With this high number of cases reporting discomfort, even if mild, at one year following treatment, raises the question of whether treatment is being directed in the correct manner or at the correct tissues. Recent research has highlighted the potential involvement of

reorganisation of the somatosensory and motor cortices in the ongoing symptoms of RC tendinopathy (Ngomo, Mercier et al. 2015).

#### **10.1.5 Heterogeneous sample**

The diagnostic criteria were based on clinical signs and symptoms that have also been commonly used in other clinical research studies on RC tendinopathy (Haahr, Ostergaard et al. 2005, Ketola, Lehtinen et al. 2013, Littlewood, Bateman et al. 2016). However, there were a proportion of participants who reported night pain and being unable to sleep on their affected shoulder. Some reported pain on a particular movement and others did not. The mechanisms of injury varied amongst the group. These differing presentations suggest the potential for a wide range of structural pathologies within the sample. With randomisation it is anticipated that these will be equally distributed between the two groups. However, it is possible that for one sub group of participants within the experimental group, the long-chain omega-3 PUFA supplements might have conferred an additional benefit but that these results became diluted due to the heterogeneous nature of the group. However, sub group analyses showed no significant differences between the treatment groups for presence of night pain, presence of constant pain, mechanism of injury or pain on movement as having an influence on outcome as measured by the OSS.

Similarly, the individual response to a fixed dose of omega -3 PUFA has been shown to vary considerably. Following supplementation for 28 days with 4g EPA and DHA, plasma EPA levels had increased by 1.1-6.36% and DHA by 3.4-6.3% (Wei and Jacobson 2011). A poor responder to supplementation might have had the effect of diluting any benefit of the long-chain omega-3 PUFA on pain and disability within the sample.

The present study showed clear increases in plasma EPA and DHA from baseline mean values of 1.2 and 2.1 % respectively to 3.7% and 3.5% on active treatment with no change in the placebo group. No evidence could be found relating the proportion of EPA and DHA in plasma lipids with decline OSS.

#### **10.1.6 Effect from common interventions**

This trial was designed to test for differences between long-chain omega-3 PUFA supplementation versus placebo. Temporal changes in symptom scores may occur with time and would be expected to improve with the exercise. It is not possible to attribute such effects

to other components of the supplements but the potential effects of the vitamin E content will be discussed.

Both supplements contained 18mg of vitamin E per day if all nine capsules were consumed. This was added to prevent the deleterious effects on vitamin E status resulting from an increased intake of long-chain omega-3 PUFAs. The UK has no dietary recommendation for vitamin E but the European Food Safety Authority (EFSA) has suggested intakes of 11 and 13 mg tocopherols equivalents/d are adequate intakes (EFSA NDA Panel (EFSA Panel on Dietetic Products 2015)). It has been suggested that greater intake of vitamin E than used in the present study might have a beneficial antioxidant effect in people with osteoarthritis (Scherak, Kolarz et al. 1990, Rhouma, de Oliveira El Warrak et al. 2013). However, there are no placebo controlled trials to support this claim in tendon related conditions. The amount of Vitamin E provided by the MaxEPA and placebo capsules was similar to that provided by the Pharma Biosport antioxidant tablet (15mg Vitamin E) alongside the fish oil capsules in the Mavrogenis (2004) and Roe (2005) studies. Roe et al (2005) found similar findings to the current RCT with no additional benefit provided by the omega 3 PUFA and antioxidant supplements, whereas Mavrogenis (2004) reported significant improvements in the treatment group.

Both treatment groups also received physiotherapy follow up over a longer period (one year) than routine treatment (usually eight weeks). In the qualitative study, follow up was reported as an enabler to continued adherence to exercise by the participants which may have had an influence on the reduction in disability and pain observed within this study. The participants were reviewed and assessed a minimum of an extra three visits above and beyond 'normal' treatment and for a further ten months than normal. During the follow up visits and assessments participants received feedback regarding their progress, informal advice and answers to any questions regarding their condition or exercises. These interactions may have resulted in improvements in pain and disability. Interaction with a physiotherapist and the therapist-patient relationship has been reported to result in a positive influence on treatment outcome (Hall, Ferreira et al. 2010). The importance and benefit of the therapist-patient relationship was also cited in the qualitative interviews where participants stated the value they placed on this relationship.

#### **10.1.7 Dose, duration and method of providing long-chain omega-3 PUFA**

Long-chain omega-3 PUFAs are normally supplied as triglyceride oils or ethyl esters and occasionally as phospholipids (Schuchardt and Hahn 2013). The material used in the present study (MaxEPA) holds a medicines' licence (PL 19488/0353) for the treatment of hypertriglyceridemia and has been used in hundreds of clinical trials including those in which inflammation was modulated. It is usually compared with olive oil placebo. MaxEPA has a well-defined formulation that is consistent with that described in the European Pharmacopoeia for fish oil rich in long-chain omega-3 fatty acids. Fish is the main dietary source of long-chain omega-3 PUFAs and it is present mainly as triglycerides. While claims have been made that phospholipid forms of long-chain omega-3 PUFA may be better absorbed and incorporated into body lipids (Ghasemifard, Turchini et al. 2014) there is a lack of evidence to support that any such differences are significant. EPA may have a greater anti-inflammatory effect than DHA (Mickleborough, Tecklenburg et al. 2009) and future studies might consider the effects of higher doses of purified EPA on the resolution of RC injury.

Several respondents stated in the survey study that the reason they have not considered taking supplements was due to the quality and balanced nature of their diet. These opinions are supported by the findings of the main clinical study.

#### **Summary**

The findings in the main clinical investigation are in keeping with the trend towards no effect in trials of long-chain omega-3 PUFA in the prevention of coronary heart disease (Nestel, Clifton et al. 2015). It is possible that the theoretical action of long-chain omega-3 PUFA on inflammation is not borne out in humans or the dose and the vehicle delivering the long-chain omega-3 PUFA is not appropriate to effect a change in symptoms in RC tendinopathy.

#### **Clinical relevance of these findings:**

The data presented in the questionnaire study (Chapter 7) suggest that one-third of people with shoulder pain take supplements, mainly fish oil containing long-chain omega-3 fatty acids. However, the findings of the randomized controlled trial presented in thesis do not support the use of long-chain omega-3 PUFA supplements in the management of RC tendinopathy. The results support the current best practice management of RC tendinopathy with exercise.

The qualitative study highlighted that longer term follow-up may improve the patient experience and enhance adherence within this group of patients. Follow-up could take the form of face to face contact, telephone calls or email interaction. The possibility of self-managing discharge from exercise class was raised providing more individualised treatment rather than a fixed number of classes for all. Pain and the perceived effectiveness of an intervention proved to be strong drivers for adherence. It is recommended that these factors are considered when prescribing a home exercise programme or treatment plan in order to maximise adherence and outcome.

A further contribution of this thesis is to add to the body of knowledge required to understand better the extent of supplement use in people diagnosed with shoulder pain. The survey study revealed that a significant percentage of patients with shoulder pain most likely will be taking dietary supplements. This should be remembered when undertaking a subjective examination and dietary supplement use should be noted alongside medications. Health professionals were the third most frequently cited source of information regarding supplements highlighting the importance of ensuring appropriate information is being provided by adequately informed practitioners.

### **Suggestions for future research**

Potential future research questions that have arisen from the work associated with this these include:

- A similar trial as the main clinical trial but using an oil rich in EPA to provide up to 5g/d without significant amounts of DHA.
- A similar trial as the main clinical trial using suitably powered to use SPADI as the primary outcome measure, taking into account the variability of the SPADI outcome measure.
- Further research is required to understand the potential impact of long-chain omega-3 PUFA on inflammation.
- Further research is needed to examine other aspects of life-style that might contribute to more rapid resolution of symptoms of rotator cuff tendinopathy including weight loss.
- A study which targets a sub-classification of participants with rotator cuff tendinopathy which may be more suggestive of active inflammatory processes eg early onset.

- A study which uses biomarkers to assess the impact of the long-chain omega-3 PUFA intervention on inflammatory markers for rotator cuff tendinopathy.
- A study which investigates whether a review appointment a few months after discharge does afford improved outcomes compared to current routine treatment.
- A study which evaluates the outcomes of increased patient choice for discharge within an exercise class for RC tendinopathy.

## **Conclusions**

One of the main findings from this thesis is that supplementation with omega 3 PUFA at 9g per day does not confer additional benefit over the recommend treatment of exercise in the treatment of individuals with RC tendinopathy. With 65% of participants within the RCT still reporting pain at one year, the search for ways to enhance treatment outcomes continues. Treatment adjuncts, lifestyle alterations and effective ways of addressing the Central Nervous System contribution to the pain all need to be considered in order to better manage the common and disabling condition of RC tendinopathy.



## **Chapter 11 : Appendices**

## Oxford shoulder Score (OSS)

### OXFORD SHOULDER SCORE

#### Problems with your shoulder

RIGHT ☐

LEFT ☐

During the past 4 weeks...

✓ tick one box for each question

<b>1</b>	During the past 4 weeks ... How would you describe the <u>worst</u> pain you had from your shoulder?				
	None	Mild	Moderate	Severe	Unbearable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>2</b>	During the past 4 weeks ... Have you had any trouble dressing yourself because of your shoulder?				
	No trouble at all	A little bit of trouble	Moderate trouble	Extreme difficulty	Impossible to do
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>3</b>	During the past 4 weeks ... Have you had any trouble getting in and out of a car or using public transport because of your shoulder?				
	No trouble at all	A little bit of trouble	Moderate trouble	Extreme difficulty	Impossible to do
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>4</b>	During the past 4 weeks ... Have you been able to use a knife and fork – at the same time?				
	Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>5</b>	During the past 4 weeks ... Could you do the household shopping on your own?				
	Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>6</b>	During the past 4 weeks ... Could you carry a tray containing a plate of food across a room?				
	Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## Oxford Shoulder Score

<b>7</b>	During the past 4 weeks ... Could you brush/comb your hair <i>with the affected arm</i> ?	Yes, Easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>8</b>	During the past 4 weeks ... How would you describe the pain you <i>usually</i> had from your shoulder?	None	Very mild	Mild	Moderate	Severe
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>9</b>	During the past 4 weeks ... Could you hang your clothes up in a wardrobe, – <i>using the affected arm</i> ?	Yes, easily	With little difficulty	With moderate difficulty	With great difficulty	No, impossible
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>10</b>	During the past 4 weeks ... Have you been able to wash and dry yourself under both arms?	Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>11</b>	During the past 4 weeks ... How much has <i>pain from your shoulder</i> interfered with your usual work (including housework)?	Not at all	A little bit	Moderately	Greatly	Totally
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>12</b>	During the past 4 weeks ... Have you been troubled by <i>pain from your shoulder</i> in bed at night?	No nights	Only 1 or 2 nights	Some nights	Most nights	Every night
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Nuffield  
Department of  
Orthopaedic Surgery

Nuffield **NHS**  
Orthopaedic Centre  
NHS Trust

## Shoulder pain and disability index (SPADI)

**SPADI**

**Shoulder Pain And Disability Index**

(Roach et al 1991)

### Part I:

Place a mark on the line to show how much **PAIN** you have had in the past week for each question.

### Example

No pain

Worst pain imaginable

---

### 1. At its worst?

No pain

Worst pain imaginable

---

### 2. When lying on the involved side?

No pain

Worst pain imaginable

---

### 3. When reaching for something on a high shelf?

No pain

Worst pain imaginable

---

### 4. When touching the back of your neck?

No pain

Worst pain imaginable

---

### 5. When pushing with the involved arm?

No pain

Worst pain imaginable

---

### Part II:

Place a mark on the line to show how much **DIFFICULTY** you have had in the past week to do the activity listed below.

### 1. Washing your hair?

No difficulty

So difficult required help

---

**2. Washing your back?**

No difficulty

So difficult required help

---

**3. Putting on an undershirt or pullover shirt?**

No difficulty

So difficult required help

---

**4. Putting on a shirt that buttons down the front?**

No difficulty

So difficult required help

---

**5. Putting on your pants?**

No difficulty

So difficult required help

---

**6. Placing an object on a high shelf?**

No difficulty

So difficult required help

---

**7. Carrying a heavy object of 10 pounds or more?**

No difficulty

So difficult required help

---

**8. Removing something from your back pocket?**

No difficulty

So difficult required help

---

## Short Form 36 (SF 36)

### SF36 Health Survey

**INSTRUCTIONS:** This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1.	In general, would you say your health is: (Please tick <b>one</b> box.)			
	Excellent	<input type="checkbox"/>		
	Very Good	<input type="checkbox"/>		
	Good	<input type="checkbox"/>		
	Fair	<input type="checkbox"/>		
	Poor	<input type="checkbox"/>		
2.	Compared to <u>one year ago</u> , how would you rate your health in general <u>now</u> ? (Please tick <b>one</b> box.)			
	Much better than one year ago	<input type="checkbox"/>		
	Somewhat better now than one year ago	<input type="checkbox"/>		
	About the same as one year ago	<input type="checkbox"/>		
	Somewhat worse now than one year ago	<input type="checkbox"/>		
	Much worse now than one year ago	<input type="checkbox"/>		
3.	The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much? (Please circle <b>one</b> number on each line.)			
	<b>Activities</b>	<b>Yes, Limited A Lot</b>	<b>Yes, Limited A Little</b>	<b>Not Limited At All</b>
3(a)	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing several flights of stairs	1	2	3
3(e)	Climbing one flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Walking more than a mile	1	2	3
3(h)	Walking several blocks	1	2	3
3(i)	Walking one block	1	2	3
3(j)	Bathing or dressing yourself	1	2	3
4.	During the <u>past 4 weeks</u> , have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u> ? (Please circle <b>one</b> number on each line.)			
		<b>Yes</b>	<b>No</b>	
4(a)	Cut down on the <b>amount of time</b> you spent on work or other activities	1	2	
4(b)	Accomplished less than you would like	1	2	
4(c)	Were <b>limited</b> in the <b>kind</b> of work or other activities	1	2	
4(d)	Had <b>difficulty</b> performing the work or other activities (for example, it took extra effort)	1	2	
5.	During the <u>past 4 weeks</u> , have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (e.g. feeling depressed or anxious)? (Please circle <b>one</b> number on each line.)			
		<b>Yes</b>	<b>No</b>	
5(a)	Cut down on the <b>amount of time</b> you spent on work or other activities	1	2	
5(b)	Accomplished less than you would like	1	2	
5(c)	Didn't do work or other activities as <b>carefully</b> as usual	1	2	

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

Not at all ☐  
Slightly ☐  
Moderately ☐  
Quite a bit ☐  
Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

None ☐  
Very mild ☐  
Mild ☐  
Moderate ☐  
Severe ☐  
Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

Not at all ☐  
A little bit ☐  
Moderately ☐  
Quite a bit ☐  
Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

(Please circle one number on each line.)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9(a) Did you feel full of life?	1	2	3	4	5	6
9(b) Have you been a very nervous person?	1	2	3	4	5	6
9(c) Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d) Have you felt calm and peaceful?	1	2	3	4	5	6
9(e) Did you have a lot of energy?	1	2	3	4	5	6
9(f) Have you felt downhearted and blue?	1	2	3	4	5	6
9(g) Did you feel worn out?	1	2	3	4	5	6
9(h) Have you been a happy person?	1	2	3	4	5	6
9(i) Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

All of the time ☐  
Most of the time ☐  
Some of the time ☐  
A little of the time ☐  
None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

(Please circle one number on each line.)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(a) I seem to get sick a little easier than other people	1	2	3	4	5
11(b) I am as healthy as anybody I know	1	2	3	4	5
11(c) I expect my health to get worse	1	2	3	4	5
11(d) My health is excellent	1	2	3	4	5

Thank You!

## **Euro Qol 5D 3L (EQ 5D 3L)**

Health Questionnaire

(English version for the UK)

(Validated for use in Eire)





By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**

- |                                       |                          |
|---------------------------------------|--------------------------|
| I have no problems in walking about   | <input type="checkbox"/> |
| I have some problems in walking about | <input type="checkbox"/> |
| I am confined to bed                  | <input type="checkbox"/> |

**Self-Care**

- |   |                          |
|---|--------------------------|
| I have no problems with self-care               | <input type="checkbox"/> |
| I have some problems washing or dressing myself | <input type="checkbox"/> |
| I am unable to wash or dress myself             | <input type="checkbox"/> |

**Usual Activities** (*e.g. work, study, housework, family or leisure activities*)

- |  |                          |
|--|--------------------------|
| I have no problems with performing my usual activities   | <input type="checkbox"/> |
| I have some problems with performing my usual activities | <input type="checkbox"/> |
| I am unable to perform my usual activities               | <input type="checkbox"/> |

**Pain/Discomfort**

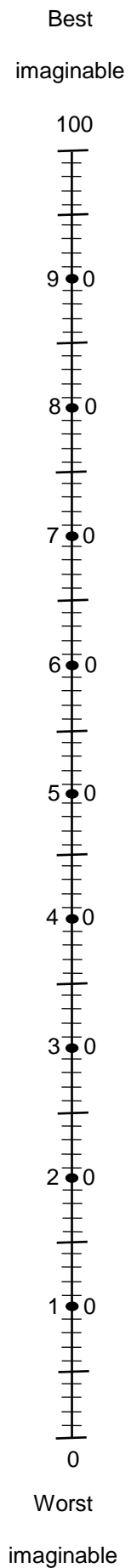
- |                                    |                          |
|------------------------------------|--------------------------|
| I have no pain or discomfort       | <input type="checkbox"/> |
| I have moderate pain or discomfort | <input type="checkbox"/> |
| I have extreme pain or discomfort  | <input type="checkbox"/> |

**Anxiety/Depression**

- |                                      |                          |
|--------------------------------------|--------------------------|
| I am not anxious or depressed        | <input type="checkbox"/> |
| I am moderately anxious or depressed | <input type="checkbox"/> |
| I am extremely anxious or depressed  | <input type="checkbox"/> |

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own  
health state**



## Patient Specific Functional Score (PSFS)

Guy's and St Thomas'



NHS Foundation Trust

St Thomas' Hospital

Physiotherapy Department

### PATIENT-SPECIFIC FUNCTIONAL SCALE

Name: \_\_\_\_\_

Date: \_\_\_\_\_

DOB: \_\_\_\_\_

☐ Baseline Assessment

☐ Follow-up Assessment

Identify up to 3 important activities that you are unable to do or have difficulty with as a result of your problem.

**Activity 1:** \_\_\_\_\_

Scoring scheme:

0      1      2      3      4      5      6      7      8      9      10

Unable to  
Perform activity

Able to perform  
activity at pre-injury level

**Activity 2:** \_\_\_\_\_

Scoring scheme:

0      1      2      3      4      5      6      7      8      9      10

Unable to  
Perform activity

Able to perform  
activity at pre-injury level

**Activity 3:** \_\_\_\_\_

Scoring scheme:

0      1      2      3      4      5      6      7      8      9      10

Unable to  
Perform activity

Able to perform  
activity at pre injury level

**Total Score = \_\_\_\_\_ (total) x 100 =**

%

## **Ethical approval for reliability study**



Hannah Dollings  
c/o Dr Matt Morrissey  
School of Biomedical & Health Sciences  
Shepherd's House, Guy's Campus  
King's College London  
SE1 1UL

18 June 2009

Dear Hannah

### **BDM/08/09-86 The intra- and inter-rater reliability of the JTech Commander PowerTrack II in the measurement of shoulder strength in asymptomatic subjects**

Thank you for sending in the amendments requested to the above project. I am pleased to inform you that these meet the requirements of the BDM and therefore that full approval is now granted. on the understanding that:

1. The sentence "There is minimal likelihood of inducing any discomfort on performing these tests on asymptomatic individuals however should it occur the assessment will be discontinued" is also added in the recruitment email and the amended recruitment email is submitted for our records

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research ([http://www.kcl.ac.uk/college/policyzone/attachments/good\\_practice\\_May\\_08\\_FINAL.pdf](http://www.kcl.ac.uk/college/policyzone/attachments/good_practice_May_08_FINAL.pdf)).

For your information ethical approval is granted until 18/06/2010. If you need approval beyond this point you will need to apply for an extension to approval at least two weeks prior to this explaining why the extension is needed, (please note however that a full re-application will not be necessary unless the protocol has changed). You should also note that if your approval is for one year, you will not be sent a reminder when it is due to lapse.

If you do not start the project within three months of this letter please contact the Research Ethics Office. Should you need to modify the project or request an extension to approval you will need approval for this and should follow the guidance relating to modifying approved applications: <http://www.kcl.ac.uk/research/ethics/applicants/modifications.html>

Any unforeseen ethical problems arising during the course of the project should be reported to the approving committee/panel. In the event of an untoward event or an adverse reaction a full report must be made to the Chairman of the approving committee/review panel within one week of the incident.

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance (<http://www.kcl.ac.uk/research/ethics/contacts.html>). We wish you every success with this work.

With best wishes

Yours sincerely

C.C.

Dr Matt Morrissey

## Participant information sheet for reliability study



### INFORMATION SHEET FOR PARTICIPANTS

*REC Reference Number: BDM/09/09-86*

#### **YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET**

**Title: The intra- and inter-rater reliability of the JTech Commander PowerTrack II in the measurement of shoulder strength in asymptomatic subjects**

We would like to invite you to participate in this original postgraduate research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

#### **Aims of the research and possible benefits**

The aim of this study is to investigate the reliability of the JTech Commander PowerTrack II in the measurement of shoulder muscle strength in asymptomatic subjects. The JTech Commander PowerTrack II is a hand held dynamometer used to measure muscle strength (also called a muscle strength testing device). If this method of testing strength of the shoulder area is proved to be reliable it will be used in physiotherapy practice to improve the assessment of patients with shoulder pain.

#### **Who are we recruiting?**

We are recruiting participants who have no history of shoulder pain and are over the age of 18 years. The exclusion criteria to taking part in the project include; pregnancy, individuals under the age of 18, those unable to give informed consent and individuals with a history of shoulder pain.

#### **What will happen if I agree to take part?**

If you agree to take part you will be asked to attend a testing session which will last for two and a half hours. During this time you will be given an opportunity to ask any questions and then be asked to sign a consent form. Your shoulder range of movement will be measured and your shoulder strength will be tested using the muscle strength testing device which is in use currently within physiotherapy practice. You will be asked move your arm into four different movements (flexion, abduction, rotation and taking your hand behind your back). You will then be asked to push against the rubberised pad of a small, hand-held machine as hard as you can three times for each of nine specific muscle groups; shoulder flexors, extensors, abductors, internal and external rotators, elbow flexors, empty can and full can tests. Each test will be measured three times before moving onto the next test. All tests will be carried out in the order stated above and will be followed by a 15 minute break. You will then be tested by the second examiner. This sequence will then be repeated by the first and then second examiner. Once you have completed all 4 strength testing sequences your involvement in the project will be complete.

**Any risks?**

The tests which are being investigated are routinely carried out in clinical practice and so the only identified risk from participating in this study would be the minimal likelihood of experiencing discomfort upon testing. Should this occur the assessment will be discontinued.

**Possible benefits**

There are no perceived benefits for the individuals taking part in the study. However it will enable clinicians to improve their assessment of shoulder conditions and therefore will have an impact on patient care. We will provide all participants with a one page summary of the results of the study if interested.

**Arrangements for ensuring anonymity and confidentiality.**

All data collected will be fully anonymised and at no point will it be traceable back to the individual. The two examiners (Hannah Dollings and Fiona Sandford) and the supervisor, Dr Matt Morrissey, will be the only persons with access to the data.

Name and contact details of the researcher:

Hannah Dollings can be contacted via Dr Matt Morrissey at the address and telephone number below.

It is up to you to decide whether to take part or not. If you decide to take part you are still free to withdraw at any time and without giving a reason.

If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form.

If this study has harmed you in any way you can contact King's College London using the details below for further advice and information:

Dr Matt Morrissey,  
Senior Lecturer of Physiotherapy,  
School of Biomedical & Health Sciences,  
Shepherds House,  
Guys Campus,  
Kings College London  
SE1 1UL  
0207 848 6678

--



## Consent form for reliability study

### CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

**Title of Study: The intra- and inter-rater reliability of the JTech Commander PowerTrack II in the measurement of shoulder strength in asymptomatic subjects**

**King's College Research Ethics Committee Ref: BDM/08/09-86**

- Thank you for considering taking part in this research. The person organizing the research must explain the project to you before you agree to take part.
- If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.
- *I understand that if I decide at any other time during the research that I no longer wish to participate in this project, I can notify the researchers involved and be withdrawn from it immediately.*
- *I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the Data Protection Act 1998.*

Participant's Statement:

I \_\_\_\_\_

agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

Signed

Date

Investigator's Statement:

---

I confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the volunteer.

Signed

Date

## Ethical approval for questionnaire study



**NHS**  
**National Research Ethics Service**  
**West London REC 3**  
Room 4W/12, 4th Floor West  
Charing Cross Hospital  
Fulham Palace Road  
London W6 8RF  
Telephone: 020 3311 7282  
Facsimile: 020 3311 7280

Dr Jeremy Lewis  
Research Lead  
Chelsea and Westminster Hospital NHS Foundation Trust  
Therapy Department  
Chelsea and Westminster Hospital  
369 Fulham Road, London  
SW10 9NH

12 July 2010

Dear Dr Lewis

**Study Title:** Shoulder pain and the use of nutritional supplements: A questionnaire based investigation.  
**REC reference number:** 10/H0706/41  
**Protocol number:**

The Research Ethics Committee reviewed the above application at the meeting held on 05 July 2010. Thank you for attending to discuss the study.

### Ethical opinion

- A. The Committee asked for clarification regarding the recruitment of participants in the study. Dr Lewis explained that as all Principal Investigators will be senior physiotherapists, patients would be approached by someone in the clinical care team.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

### Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

### Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.*

This Research Ethics Committee is an advisory committee to London Strategic Health Authority  
The National Research Ethics Service (NRES) represents the NRES Directorate within  
the National Patient Safety Agency and Research Ethics Committees in England

*Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

*Sponsors are not required to notify the Committee of approvals from host organisations.*

**It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

#### **Approved documents**

The documents reviewed and approved at the meeting were:

<b>Document</b>	<b>Version</b>	<b>Date</b>
Investigator CV		
Protocol	1	03 March 2010
Letter from Funder		14 May 2010
Student CV: Fiona Sandford	1	24 April 2008
REC application	2890/123712 /1/988	26 May 2010
Covering Letter		26 May 2010
Questionnaire	1	01 August 2009
Advertisement	1	01 May 2010
Participant Information Sheet	1	21 April 2010
Participant Consent Form	1	21 April 2010
Referees or other scientific critique report		18 May 2010

#### **Membership of the Committee**

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

#### **Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

#### **After ethical review**

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

This Research Ethics Committee is an advisory committee to London Strategic Health Authority  
The National Research Ethics Service (NRES) represents the NRES Directorate within  
the National Patient Safety Agency and Research Ethics Committees in England

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email [referencegroup@nres.npsa.nhs.uk](mailto:referencegroup@nres.npsa.nhs.uk).

**10/H0706/41**

**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely



**Dr Sabita Uthaya**  
**Chair**

Email: [louise.moran2@imperial.nhs.uk](mailto:louise.moran2@imperial.nhs.uk)

*Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments  
"After ethical review – guidance for researchers"*

*Copy to: Mary Anne Tourette*

**Participant information sheet for questionnaire study**  
**PARTICIPANT INFORMATION SHEET**

V1 dated 21.4.2010

**Study title “Shoulder pain and the use of nutritional supplements”:**

**A questionnaire based investigation.**

**2. Invitation paragraph**

You are being invited to take part in a research study that is aiming to investigate if people with shoulder pain use nutritional or food supplements; such as vitamins and fish oils, to help with symptom control and management of the condition. This investigation involves a questionnaire which will take approximately 30 minutes to complete. After that your involvement in this study will be complete. No identifiable personal data will be collected and no-one will know what you wrote. Before you decide to participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP or Consultant if you wish. Please ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part. This study forms part of a PhD (Doctoral) degree programme.

**3. What is the purpose of the study?**

Many people take nutritional and food supplements for musculoskeletal problems including those involving the shoulder region. However, very little research has been conducted to determine what affect they actually have. We are interested in learning from people who currently have shoulder pain about their experiences with nutritional/ food supplements. This includes views from people who regularly take food supplements, people who have tried them only once or twice, and from people who have never taken them.

**4. Why have I been chosen?**

We have approached you because you have shoulder pain and we are interested in learning about your views and experiences with nutritional/ food supplements.

## **5. What will happen to me if I take part?**

If, after reading this information document you would like to participate, the principal investigator will ask you to complete a consent document. This is a formal requirement for all research studies. After completing the consent form you will be given an envelope containing the questionnaire. The questionnaire booklet should take approximately 30 minutes to complete. Once completed the questionnaire booklet is placed back in the envelope which you may seal and hand back to the principal investigator. You may fill these forms in before or after your treatment or if you prefer you may take them home and complete them there and bring them when you return next time. The questionnaires contain no information that can identify you personally and you are under no obligation to participate in this study. Not participating will not affect the treatment you receive in any way.

## **6. What do I have to do?**

If you agree to participate you will need to follow the procedure outlined in section 5.

## **7. What is the procedure that is being tested?**

We are not testing any new products or procedures in this study, we only wish to learn about your experiences with nutritional/ food supplements. This may range from considerable experience to no experience at all.

## **8. What are the side effects of taking part?**

As this is a questionnaire based study we do not perceive that there will be any side effects if you take part. Completion of the questionnaire should take approximately 30 minutes.

## **9. What are the possible disadvantages and risks of taking part?**

There are no disadvantages or risks for those taking part in this study.

## **10. What are the possible benefits of taking part?**

We hope that this research will provide a greater understanding about the use and perceived benefits of taking nutritional/ food supplements for people who are experiencing shoulder pain.

**11. What if something goes wrong?**

We do not anticipate that anything will go wrong in this study as we are not trying any new procedure. This is a questionnaire based study.

**12. Will my taking part in this study be kept confidential?**

All information which is collected about you during the course of the research will be kept strictly confidential and no personal or identifiable information about you is collected in the questionnaires.

**13. What will happen to the results of the research study?**

We hope to use the information we obtain from this study to inform other health professionals about our results. We therefore ask your permission to publish the data we obtain. The results will probably be published about one year after the end of the study. If you are interested in finding out about our results, you may contact the Physiotherapy Department where you are receiving treatment to enquire about the findings and a summary will be made available to you through the postal service or via email from the chief investigator. If you so wish you may also discuss the findings with the chief investigator once the results have been published.

**14. Who is organising and funding the research?**

The main sponsor for this study is the Chelsea and Westminster Hospital NHS Foundation Trust.

**15. Who has reviewed this study?**

This study has been reviewed by NHS ethics but also by the local practice ethics committee.

**16. Contact for further information**

Fiona Sandford, Lead research physiotherapist on 07836 622076 or  
Fiona.sandford@kcl.ac.uk

**17. For ethical or medical reasons recommendations are sometimes made for certain people not to participate in a specific research investigation. We will ask everyone participating in this study the following questions.**

In this investigation we will only include people who;

- (i) have had shoulder pain for more than one month and



(ii) are older than 18 years of age.

**18. After you have read this information sheet**

Please take your time in order to decide if you would like to participate or not. If you wish please discuss your possible involvement with family, friends and other health professionals.

If you agree to participate in this study, we will ask you to fill in and sign a Research Consent Form, in front of someone who will witness the signature. This will be done before you are given the questionnaire. You may complete the questionnaire in the clinic or at home. If you wish, please keep this information sheet.

If you choose not to participate your treatment will not be affected in any way. You may decline from participating at any stage (even after you have signed the consent form) and you do not have to give a reason.

**Thank you for taking the time to read this information sheet.**

## Consent form for questionnaire study

### Research Participant Consent Form

**Title of Project:**      **Shoulder pain and the use of nutritional supplements:**  
**A questionnaire based investigation.**

---

## Participant Declaration

**Please initial box  
if correct**

I have been given the chance to read and understand the information sheet (V1 dated 21.4.2010) relating to the above study.

☐

I have been given the opportunity to ask questions and discuss the study.

☐

I have been made aware of the risks/ benefits.

☐

I understand that I am free to withdraw from this study at any time without prejudice to my future care/ treatment.

☐

I understand that as this is an anonymous questionnaire study there are no compensation procedures / policies in place, other than routine NHS compensation procedures.

☐

I am over 18 years of age and I have had shoulder pain for more than 1 month.

☐

**Title of Project:**        **Shoulder pain and the use of nutritional supplements:**  
                                 **A questionnaire based investigation.**

I agree to take part in the above study

Signature .....

Name .....

Date .....

**Person responsible for obtaining Informed Consent:**

'To the best of my knowledge I have provided the above individual with sufficient information to enable them to give informed consent'.

Signature .....

Name .....

Date .....

Position.....

Witnessed by:

Signature .....

Name .....

Date .....

**SHOULDER PAIN AND  
NUTRITIONAL  
SUPPLEMENTS:  
WHAT ARE PEOPLE  
USING?**

**Questionnaire Booklet**

### **Instructions for use of the questionnaire booklet**

The aim of these questionnaires is to find out which nutritional supplements, if any, people with shoulder pain are taking and what their experiences and beliefs are regarding these supplements. The study will also provide information on severity of shoulder pain and general health. The full details of this study are included in the information sheet given to you by the principal investigator.

Most of the questions can be answered by ticking a box or circling a number.

Please read the instructions on each questionnaire and answer every question, even if you are unsure of your answer.

When you have finished:

- Please check you have answered every question
- Please discuss any questions you have with the principal investigator
- If you require any further information, or if you have any questions on this project, please contact Kate Esden 020 8630 3527 or Dr Jeremy Lewis on 020 3315 8406

All responses to these questionnaires will be treated in the strictest confidence.

**Your participation in this research project is very much appreciated**

## Shoulder pain and nutritional supplements study (V1 1.8.2009)

Dear Participant,

Thank you for agreeing to participate in this study.

We are interested in finding out if people who are suffering from shoulder pain are taking food / nutritional supplements (*e.g. vitamins, fish oils, etc*) to help manage their pain. We will not ask you for any identifiable personal information and all the information we collect will be kept confidential. The total time required will be approximately 30 minutes. If you have any questions please ask the person who gave you this questionnaire. As you are aware you may withdraw from this study at anytime, without giving a reason and your decision to do this will not affect the treatment you receive.

**Thank you once again for your time.**

**Today's date:** (day/month/year)    \_\_\_\_ / \_\_\_\_ / **20** \_\_\_\_

**Your age:** \_\_\_\_ years                      **Gender:** (please circle)    Male   /   Female

**Your height** (if known):                      \_\_\_\_ (please state feet and inches, or metres)

**Your weight** (if known):                      \_\_\_\_ (please state stones and pounds or kilograms)

**Ethnicity:** (please place tick ✓ in empty space next to appropriate ethnic background)

1.	Asian - Indian		4.	Asian – Any other Asian background. <i>Please state:</i>	
2.	Asian - Pakistani				
3.	Asian - Bangladeshi				
5.	Black - Caribbean		7.	Black – Any other Black background. <i>Please state:</i>	
6.	Black - African				
8.	Mixed - White and Black Caribbean		11.	Mixed – Any other Mixed background. <i>Please state:</i>	
9.	Mixed - White and Black African				
10.	Mixed - White and Asian				
12.	White - British		14.	White – Any other White background. <i>Please state:</i>	
13.	White - Irish				
15.	Chinese		16.	Japanese	
17.	Middle Eastern – <i>Please state:</i>		18.	Any other Ethnic background – <i>Please state:</i>	
19.	Prefer not to state Ethnic background				

**Shoulder pain:**                      **How long have you had your shoulder pain?**

(please circle one of the following)

**0-6 weeks**

**6 weeks to 3 months**

**More than 3 months**

## Education and Employment

Please tick the box for each heading that is most appropriate for you.

Type of work (employed only)	Manual	
	Non-manual	
	Not sure	
Unable to work because of shoulder problem	Yes	
	No	

Education	None	
	Secondary	
	Higher	
Employment	Full time	
	Part time	
	Homemaker	
	Retired	
	Unemployed	

Preferred sleeping position: \_\_\_\_\_

Please complete either the **No box-** if you are **not currently taking a supplement**

or the **Yes box (on the next page - page 5)-** if you are **currently taking any supplements**.

### **No** – I am not currently taking any food / nutritional supplements

Please tick ✓ all those that apply to you.

1. I don't believe in taking food / nutritional supplements \_\_\_\_\_
2. There is no evidence / scientific basis for taking them \_\_\_\_\_
3. I am scared of any side effects \_\_\_\_\_
4. I have tried them but they didn't help \_\_\_\_\_  
What did you try?
5. I would like to take them but they are too expensive \_\_\_\_\_
6. I would like to take them but I don't know what to take \_\_\_\_\_
7. I don't know what food / nutritional supplements are \_\_\_\_\_
8. Anything else (please tell us anything else you think is relevant for us to know about your experiences / beliefs relating to food / nutritional supplements)

Thank you for completing this section, please now complete the additional questionnaires starting on page 7



Yes, I am currently taking food/nutritional supplements. For those taking supplements please complete page 5.

Please answer all questions as best you are able. (continue to write on the back of the page if required).

1. Please list all the food / nutritional supplements/ number each day / dose / and reason for taking

Name of supplement	Dose	Number each day	Purpose	How long have you been taking this supplement?
<b>Example:</b> Vitamin C	120mg	1 tablet each day	For my immune system	6 months
<b>Example:</b> Glucosamine	500mg	2 tablets each day	For joint pain	8 months
<b>Please list <u>all</u> the supplements you are taking (please write on back of this page if required)</b>				

2. Of the supplements you listed above, which ones are you taking for your shoulder pain?

3. What is the benefit they are having for your shoulder pain? (please circle the one most correct answer)

None      Minimal      Good      Very good      Excellent

4. Where did you first learn about these supplements?

(Examples: friend/ colleague/ Internet/ publication (and what type)/ health professional (who) / radio / TV / pharmacy / health shop – please detail all that apply)

5. Please estimate the average monthly cost of the supplement(s) you are taking for your shoulder?

6. Would you recommend these supplements to others? (please circle the one most correct answer)

No      Unsure      Yes

7. Please list any side effects you have experienced that you attribute to the supplement(s) you are taking for your shoulder?

8. Anything else (please tell us anything else you think is relevant for us to know about your experiences / beliefs relating to food / nutritional supplements)

The Oxford Shoulder Score, Shoulder Pain and Disability Index, Euro QoL 5D 3L and SF 36 followed on in the booklet but can be seen in Appendices 11.1-11.4



## Ethical approval for RCT

### Bromley Local Research Ethics Committee

Bromley PCT, Bassetts House,  
Broadwater Gardens  
Farnborough  
Kent  
BR6 7UA

Telephone: 01689 880592

Facsimile: 01689 855662

22 May 2008

Mrs Fiona Sandford  
Clinical Specialist Physiotherapist  
Guys and St Thomas' NHS Foundation Trust  
Physiotherapy Department, 3rd Floor  
Lambeth Wing, St Thomas' Hospital,  
Lambeth Palace Road,  
London SE1 7EH

Dear Mrs Sandford

**Full title of study:** Randomised single-blinded placebo-controlled study investigating the role of poly-unsaturated fatty acids in addition to exercise in the management of rotator cuff (rc) tendinopathy.

**REC reference number:** 08/H0805/21

The Research Ethics Committee reviewed the above application at the meeting held on 15 May 2008. Thank you for attending to discuss the study.

#### Ethical opinion

1. Members agreed that the reference to CERES in the Participant Information Sheet should be deleted as this body no longer exists. You agreed to remove this.
2. Members noted that the Participant Information Sheet stated that participants with communication difficulties would be excluded, although this was contrary to A33-1 of the application form. You stated that these participants could be included in the study and agreed to amend the Participant Information Sheet accordingly.

Members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

### **Ethical review of research sites**

The Committee agreed that all sites in this study should be exempt from site-specific assessment (SSA). There is no need to submit the Site-Specific Information Form to any Research Ethics Committee. The favourable opinion for the study applies to all sites involved in the research.

### **Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

### **Approved documents**

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Application		07 April 2008
Investigator CV		24 April 2008
Protocol	2	24 April 2008
Covering Letter		22 April 2008
Peer Review		25 February 2008
Statistician Comments		18 October 2007
Questionnaire: SF36 Health Survey		07 April 2008
Questionnaire: SPADI		07 April 2008
Questionnaire: EQ-5D		07 April 2008
Questionnaire: Oxford Shoulder Score		07 April 2008
Advertisement	1	04 April 2008
GP/Consultant Information Sheets	1	02 April 2008
Participant Information Sheet: I version for each site	1	02 April 2008
Participant Consent Form: 1 version for each site	1	02 April 2008
CV for Catherine Collins		24 April 2008
CV for Professor Tom Sanders		24 April 2008
CV for Matt Morrisey		24 April 2008

CV for Professor Axford		24 April 2008
CV for Jeremy Lewis		24 April 2008
Data collection sheet	1	02 April 2008
Food, drink & supplement record	1	02 April 2008
Letter from St Georges MRC		01 April 2008
Email from W Vasdias (Seven Seas)		31 October 2007
Shoulder Class Information	1	23 April 2008
Flow Chart	1	02 April 2008
Email from MHRA		11 April 2008
Shoulder Class Patient Information Booklet	1	02 April 2008
Research participants' exercise and tablet diary	1	04 April 2008
Peer review		22 November 2007
Peer review		12 November 2007

### **Membership of the Committee**

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

### **Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

### **After ethical review**

Now that you have completed the application process please visit the National Research Ethics Website > After Review

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- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email [referencegroup@nres.npsa.nhs.uk](mailto:referencegroup@nres.npsa.nhs.uk).

**08/H0805/21**

**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely



**Ms Carol Jones**

**REC Chair**

Email: [janine.peters@bromleypct.nhs.uk](mailto:janine.peters@bromleypct.nhs.uk)

## Participant information leaflet for RCT



**St Thomas' Hospital**  
Physiotherapy Department  
Third Floor Lambeth Wing  
St Thomas' Hospital  
Lambeth Palace Road  
London SE1 7EH  
Tel: 020 7188 4174  
**Mobile : 07836 622086**  
**Fiona.sandford@kcl.ac.uk**

### PARTICIPANT INFORMATION SHEET

Version 3. 05.11.08

#### 1. Study title

**A Randomised single-blinded placebo-controlled study investigating the role of poly-unsaturated fatty acids in addition to exercise in the management of rotator cuff (rc) tendinopathy.**

R&D Ref No: 08/H0805/21

#### 2. Invitation paragraph

You are being invited to take part in a research study that is aiming to investigate if poly-unsaturated acids (also known as fish oils or omega 3s) is helpful in the treatment in the shoulder tissues of people who have been diagnosed with problems of the rotator cuff (muscles and tendons of the shoulder).

Before you decide to participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP or Consultant if you wish. Please ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

#### 3. What is the purpose of the study?

Shoulder pain is extremely common. One of the main causes of shoulder pain involves problems of the 4 deep tendons or the shoulder (known as the rotator cuff tendons) and a fluid filled sack that normally sits above these tendons to make shoulder movement occur more easily. There are a number of causes of shoulder pain relating to these tissues ranging from inflammation to degeneration. Currently there are

many different treatments for this condition. One widely accepted treatment is exercise and manual therapy (joint mobilisations performed by a physiotherapist). Some patients have reported that they have found benefit from taking supplements containing poly-unsaturated fatty acids (also known as fish oils or omega 3s). If a significant difference can be seen in those who take the supplements it may lead to new treatments for these conditions.

The purpose of this study is to determine if taking supplements containing poly unsaturated fatty acids (also known as fish oils or omega 3s) has a beneficial effect on function and pain for people who have been diagnosed with problems of the rotator cuff.

#### **4. Why have I been chosen?**

Most probably you will be reading this document because you have shoulder pain that has been diagnosed as involving the shoulder tendons.

Poly-unsaturated fatty acids (also known as fish oils or omega 3s) have been shown to have positive effects on heart disease, rheumatoid arthritis and on tendon conditions in athletes. Therefore it was believed that they might also help those with tendon problems of the shoulder. The supplements will be supplied by a company called seven seas which is a well known company on the high street and also supplies the NHS with prescribed supplements. The exercise class and home exercise programme which you will undertake is part of the normal treatment you would receive from your Physiotherapist.

We are approaching you because we would like to determine how if taking a supplement supplied by seven seas containing poly unsaturated fatty acids (also known as fish oils or omega 3s) has a beneficial effect on pain and outcome in people with shoulder tendon problems. You will be one of a number of people who will be included in this investigation. We guarantee that no-one will be able to identify you in the published results and your participation will remain anonymous.

#### **5. What will happen to me if I take part?**

If you are interesting in participating in this study we will give you this patient information document to take and read. We would recommend that you take your time to consider involvement with this study and you may choose to discuss your possible involvement with family and friends. You may choose to discuss this with other healthcare professionals and if you wish, you are also welcome to discuss your involvement with the Lead Investigator of this study, Fiona Sandford. Fiona Sandford's contact information is on the top of this form and if you allow she will contact you to discuss any questions and to confirm or cancel (if you chose not to take part) your assessment with her. If you do not wish to be contacted you are free to still attend the assessment with the Lead Investigator and still be a part of the study.

If you agree to participate you will be asked to sign a consent form at the time of your shoulder assessment. If you sign the form we will perform a series of tests and fill in some questionnaires that will take about 30 minutes. These tests will examine the range of movement of your shoulder joint and the strength of your shoulder muscles. They will be the same tests you initially had before your diagnosis was made. The reason why we are repeating them just before you start the treatment is so that we have an accurate baseline level of your shoulder problem to then compare any improvements to. Some of these tests may cause pain or some discomfort but they are routine tests used in clinics to make a diagnosis of shoulder tendon problems. Following the tests you will be asked to have a blood test. This tells us the level of essential fats in your blood. It will be taken by a specialist nurse or phlebotomist (a health care professional who takes blood). They will take a 5ml sample (the amount of a tea spoon). This blood will be tested in a laboratory and then destroyed. It will not be kept nor any other tests run on it. Again it will not be identifiable to your name.

You will then attend the shoulder class the following week. Here you will be given your supplements to take home. These supplements will either contain poly-unsaturated fatty acids (also known as fish or omega 3s) 170mg eicosapentaenoic acid (EPA), 115mg docosahexaenoic acid (DHA) and anti-oxidants (100 units/g Vitamin E and 10units/g Vitamin D) or a mixed oil and the anti-oxidants (100 units/g Vitamin E and 10units/g Vitamin D). You will be asked to take whichever supplement you are allocated for a total of 8 weeks. During this time you will be asked to record your supplement taking in your study diary. You will have a home exercise programme which we will ask you to carry out once a day. We will also ask you to record what exercises you completed and how you felt. You will also be attending the shoulder class once weekly.

At the end of the 8 week class you will be reassessed. Again we will perform the same tests and questionnaires you had at the start of the programme. Again this will take approximately 30 minutes. You will also be asked to go for another blood test so that we can compare the levels of fats in your blood. This blood test will be the same as the test you had at the start.

We will then ask you to return to be re-assessed at 3, 6 and 12 months from your start date in the class. This is to reassess you again using the same tests and questionnaires as we did at the beginning but not the blood tests. As we are asking you to return for these extra assessments we will reimburse you for your travel expenses if required (up to the value of a travel card).

Following this your involvement with this study will be over.

If you decide not to participate you will not be required to sign the research consent form and you will have treatment on your painful shoulder. Not participating in this research will not effect your treatment in any way and it is up to you whether you participate or not.

## **6. What do I have to do?**

The first thing you need to do is decide if you would like to participate or not. This is entirely your decision and deciding not to participate will not affect the quality of your care. If you do decide to participate you will need to follow the procedure outlined in section 5.

## **7. What is the procedure that is being tested?**

We are trying to determine if poly unsaturated fatty acids (also known as fish oils or Omega 3s) have a beneficial effect on function in patients with rotator cuff disease.

## **8. What are the side effects of taking part?**

Polyunsaturated fatty acids (also known as fish oils or Omega 3s) are known to be safe in the doses being used in this trial. Reported side effects have included an upset stomach or stomach pain, black tarry stools, bruising and heartburn. If you were to feel any of these symptoms we ask you to stop taking the tablets and either see your Gp or call the lead investigator Fiona Sandford for further advice.

Some of the shoulder tests may be painful. In most cases this will be similar to the pain you are experiencing in your shoulder. The tests are used to determine which structure or structures are involved with your pain. Sometimes this changes over time and that is why we would like to re-examine your shoulder prior to you starting the shoulder class.

The blood test may be uncomfortable but the health care professionals are trained to take blood and a very small sample is going to be taken.

## **9. What are the possible disadvantages and risks of taking part?**

There are no perceived disadvantages or risks for those taking part in this study. The examination procedures are ones used routinely in the clinical examination of the shoulder. They may be associated with some discomfort or pain during the tests. If any side effects of the supplements are experienced, we recommend that the supplements are stopped immediately.

## **10. What are the possible benefits of taking part?**

We hope that this research will help us eventually help relieve pain in shoulder pain syndromes. It might



help other patients with shoulder pain by eventually learning new ways of treating this common problem. However, as with all research, this cannot be guaranteed.

**11. What if something goes wrong?**

We do not anticipate for anything to go wrong in this study as we are not trying any new procedure or supplement, we are simply investigating if an existing supplement has a benefit in patients who have been diagnosed with rotator cuff tendon problems.

However, if you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms may be available to you.

**12. Will my taking part in this study be kept confidential?**

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital relating to this study will have your name and address removed so that it will not be possible to recognise you from it.

If you do participate your GP (and Consultant if appropriate) will be sent a letter notifying them of your participation in this study (if you give your permission for this letter to be sent).

**13. What will happen to the results of the research study?**

We hope to use the information we obtain from this study to inform other health professionals about our results. We therefore ask your permission to publish the data we obtain. However, we guarantee to keep your name and identity confidential and this will not be made available to anyone at any stage. The results will probably be published about one year after the end of the study and if you are interested in finding out about our results, we would be happy to send you a one page summary of our findings.

**14. Who is organising and funding the research?**

This research is a collaborative study between the Physiotherapy and Dietetics and Nutrition departments at both Guys and St Thomas' Foundation NHS Trust and St George's Foundation NHS Trust.

**15. Who has reviewed this study?**

This study has been reviewed by international experts. In addition it has been reviewed by the Hospital's Research and Development committees and Bromley Ethics Committee.

**16. Contact for further information**

If you would like any further information about this study, please feel free to contact Fiona Sandford, Clinical Specialist Physiotherapist, on telephone number 0207 188 4174 or 07836 622076, or e-mail [Fiona.sandford@kcl.ac.uk](mailto:Fiona.sandford@kcl.ac.uk).

**17. Most research projects recommend that certain patients don't participate in a specific study. This is usually for ethical or medical reasons. We will ask everyone participating in this study the following questions.**

Are you younger than 18 years of age? Yes No

Are you pregnant, suspect you are pregnant,  
or attempting to become pregnant? Yes No

**If you answer yes to any of these questions we will thank you for taking time to consider this study but we will be unable to include you in this research.**

We will also be conducting clinical tests to ensure that you have not got any other shoulder condition that requires different treatment. If you have you will be offered the appropriate management for that condition. This will mean that you will not be able to participate in this study.

**If you are a patient and decide to participate in this research (and are eligible to participate) then we will also ask you if you would like us to send a letter to your GP or consultant, informing them that you are participating in this study.**

**18. After you have read this information sheet**

Please take your time in order to decide if you would like to participate or not. If you choose please discuss your possible involvement with family, friends and other health professionals.

If you agree to participate in this study, we will ask you to fill in and sign a Research Consent Form, in front of someone who will witness the signature. This will be done at the time of your assessment. At the same time we will re-test your shoulder with muscle strength tests and measure how much movement there is available in your shoulder. You will then be asked to have the blood test. This will take place just after the assessment.

If you wish, please keep this information sheet.

If you choose to participate we will give you a copy of your signed consent form.

If you choose not to participate you will go ahead with your physiotherapy treatment and your decision not to participate will not affect your treatment.

**Thank you for taking the time to read this information sheet.**

Consent form for RCT

Guy's and St Thomas'



NHS Foundation Trust

St Thomas' Hospital

Physiotherapy Department

Third Floor Lambeth Wing

St Thomas' Hospital

Lambeth Palace Road

London SE1 7EH

Tel: 020 7188 4174

Fax: 020 7188 4166

Research Subject Consent Form

**Title of Project: A Randomised single-blinded placebo-controlled study investigating the role of poly-unsaturated fatty acids in addition to exercise in the management of rotator cuff (rc) tendinopathy.**

Protocol Version: **Version 1 date** 02.04.08

Local Research Ethics Number: 08/H0805/21

Patient Hospital Number:

Patient Study Identification Number:

Patient Initials:

---

**Participant Declaration**

**If Correct**

**Please initial box**

I have been given the chance to read and understand the information sheet (dated 02.104.08- Version1) relating to the above study

I have been given the opportunity to ask questions and discuss the study.

I have been made aware of the risks/ benefits

I understand that authorised individuals may look at my medical notes and give permission for these individuals to have access

I understand that I am free to withdraw from this study at any time without prejudice to my future care/ treatment

I have had the compensation procedures explained to me

☐

I would like my GP or consultant to know that I am participating in this research project.

☐

I would like to receive a one page summary of the findings of this study.

☐

**Title of Project: A Randomised single-blinded placebo-controlled study investigating the role of poly-unsaturated fatty acids in addition to exercise in the management of rotator cuff (rc) tendinopathy.**

Local Research Ethics Number:

Patient Hospital Number:

I agree to take part in the above study

Signature .....

Name .....

Date .....

**Person responsible for obtaining Informed Consent:**

'To the best of my knowledge I have provided the above individual with sufficient information to enable them to give informed consent'.

Signature .....

Name .....

Date .....

Position .....

**Witnessed by:**

Signature .....

Name .....

Date .....

Four day food diary

Guy's and St Thomas'



NHS Foundation Trust

St Thomas' Hospital

Physiotherapy Department

Third Floor Lambeth Wing

St Thomas' Hospital

Lambeth Palace Road

London SE1 7EH

Tel: 020 7188 4174

# Food, drink & supplement record

Version 1 date: 02.04.2008

Name: \_\_\_\_\_

Date of 1<sup>st</sup> Shoulder Class \_\_\_\_\_

Date of 2<sup>nd</sup> Assessment \_\_\_\_\_

Date of 3<sup>rd</sup> Assessment \_\_\_\_\_

Date of 4<sup>th</sup> Assessment \_\_\_\_\_

Date of 5<sup>th</sup> Assessment \_\_\_\_\_

# Food, Drink & Supplement record

## Why do I need to keep a dietary record?

It is important prior to starting the trial that we know your normal intake. This will be used to support and help explain any results are found in the trial. A Registered Dietitians (RDs) will assess the food diary at the end of the trial.

This food diary will help you record what you eat, drink and any supplements that you might take.

Please be as honest as possible. Please also complete it for 2 work or 'usual' days and 2 weekend days or days off.

## How do I keep a dietary record?

Imagine that you are trying to describe an item of clothing to a friend. For them to 'picture' it they would have to be given some details. For example, if you describe a shirt as made of fine cotton with fine pale blue stripes and a small collar, then it would give your friend much more of an idea as to what you are describing.

The same applies to keeping a dietary record. If you just write a 'shopping list' of foods, it's difficult to determine how much, or what type of food that you normally eat.

So a good diary describes what you normally eat or drink, so that when the dietician looks at it, it's easy to work out what you ate. The main points of a good diary are:

### 1. How much food or drink?

What would you describe as a portion of chicken? A leg, a quarter, a large breast, or 4 wings? Make it easier for the dietician by describing what **your** normal portion is.

If you eat prepared foods, then just write down the weight on the packet, and whether you ate all of the contents or just some. e.g 1 chicken kiev, (Tesco, box of two 250g)

### 2. What type of food or drink?

- **Bread** is a popular food available in many varieties: white, brown, wholemeal, bread rolls or sliced bread –

- thick, medium or thin cut.
- **Milk** could be full fat, semi or fully skimmed, evaporated milk or dried powder.
- **Cereal** could be cornflakes, branflakes, Weetabix, porridge oats or muesli.

Please help the dietitian by explaining what type of food you eat. If you only eat one sort of bread, list it once and then any 'bread' entry will be assumed to be the same type.

## Food, Drink & Supplement record

**Typical food and drink intake:**

<i>Usual day (your diet most of the time eg during a working week)</i> <b>Day 1</b>	<i>meal</i>	<i>Weekend/ alternate day</i> <i>(other food and drink choices)</i> <b>Day 2</b>
	<b>Breakfast:</b>	
	<b>Mid-morning</b>	
	<b>Lunchtime</b>	
	<b>Mid-afternoon</b>	
	<b>Evening meal</b>	
	<b>Evening /bedtime drinks/ snacks</b>	



## Food, Drink & Supplement record

**Typical food and drink intake:**

<i>Usual day (your diet most of the time eg during a working week)</i>  <i>Day 3</i>	<i>meal</i>	<i>Weekend/ alternate day (other food and drink choices)</i>  <i>Day4</i>
	Breakfast:	
	Mid-morning	
	Lunchtime	
	Mid- afternoon	
	Evening meal	
	Evening/ bedtime drinks/snacks	

## **Food, Drink & Supplement record**

### **What else do you take?**

It's common for people with arthritis to take nutritional supplements along with medication for their arthritis or other health conditions.

It would help your dietician if you could list any supplements or medicines you take:







#### **Supplements include:**

Any vitamin, mineral, herbal or homeopathic supplement, in liquid or tablet form. Please list the name of the supplements, the manufacturer (who name of the company who make or sell them) and the amount you take each day:

#### **What medicines do you take?**

These are the medicines you obtain on prescription from your GP or hospital doctor.

## Email regarding oxidation status of supplements at end of study

 Reply all |   Delete |  Junk |  ... 

**From:** willem.vasdias@merckgroup.com <willem.vasdias@merckgroup.com>  
**Sent:** 23 September 2013 08:57  
**To:** Sanford, Fiona  
**Subject:** RE: Capsules

Good morning Fiona

I tried to contact you last Friday. You must have known!

I can only apologise, once again, for this delay. The fatty acid composition of the capsules you returned confirmed that the Maxepa capsules were indeed Maxepa. The levels of EPA and DHA were within specification which indicates that no oxidation had taken place. EPA and DHA would have been amongst the first fatty acids to go when the oil starts to oxidise. The appearance of the oil was as expected.

I hope that this is satisfactory. The lab informs me that there are no further capsules from the tubs you returned so additional analyses are not possible.

Please contact me if you have any comments or comments.

With kind regards

Willem

Dr F Willem Vas Dias  
Nutritionist  
=====

Seven Seas Limited  
Registered in England under Co No:00351663  
Registered Office: Hedon Road, Hull HU9 5NJ  
Tel.: 01482 716298  
Mobile: 07789597397  
Email: willem.vasdias@merckgroup.com  
<http://www.seven-seas.com>

Assessment form- baseline

***A Randomised single-blinded placebo-controlled study investigating the role of poly-unsaturated fatty acids in addition to exercise in the management of rotator cuff (rc) tendinopathy.***

**Data Collection Sheet**

(version 2 date 29.09.2008)

<p><i>Sticker if available</i></p> <p>Name: _____</p> <p>Hospital Number: _____</p>
---

Participant Number: \_\_\_\_\_

Today's date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Symptomatic shoulder: Right / Left

Duration of symptoms: Years \_\_\_\_\_

Months \_\_\_\_\_ Weeks \_\_\_\_\_ Days \_\_\_\_\_

Onset: trauma / non-traumatic      How?: \_\_\_\_\_

Nature of symptoms (*tick appropriate*):    Constant pain ☐    Intermittent pain ☐

Pain increases with movement: yes / no      If yes, main movement \_\_\_\_\_

Is night pain present: yes / no      If yes, is it possible to sleep on painful side?    yes / no

On a scale of 0-10 (where 0 = 'no pain' and 10= the worst imaginable pain') where would you place your pain on that scale?                      /10

Inclusion criteria [tick if present]  [circle those present]	Exclusion criteria [tick if present]
<input type="checkbox"/> Over 18 years of age	<input type="checkbox"/> Cervical movements reproduce shoulder symptoms
<input type="checkbox"/> Unilateral symptoms	<input type="checkbox"/> History of shoulder subluxations / dislocations
<input type="checkbox"/> Shoulder pain on flexion / or abduction	<input type="checkbox"/> Known allergy to fish or fish products
<input type="checkbox"/> Pain on Neer sign and / or Hawkins and Kennedy Test	<input type="checkbox"/> Systemic illnesses, Diabetes, RA
<input type="checkbox"/> Pain on resisted abduction and / or ER, and / or 'full cans' and / or 'empty cans'	<input type="checkbox"/> Radiographic or clinical evidence of shoulder instability
<input type="checkbox"/> Pain on palpation of gtr tuberosity of humerus.	<input type="checkbox"/> Unwilling to take fish oils
	<input type="checkbox"/> Pregnant or attempting to become pregnant or breast feeding
	<input type="checkbox"/> Currently involved in another research investigation
	<input type="checkbox"/> Currently taking over 1g of active ingredient fish oils.

**Medications/Allergies:**

**Other comments:**

<b>Weight:</b>	<b>Height..... BMI.....</b>
<b>Smoker: No.....Yes    how many per day.....</b>	

## Clinical Findings

Painful shoulder (circle)	<b>Left</b>	<b>Right</b>
Oxford Shoulder Disability Score		/ 48
SPADI Score		
EQ-D5 Score		
SF-36 Score		

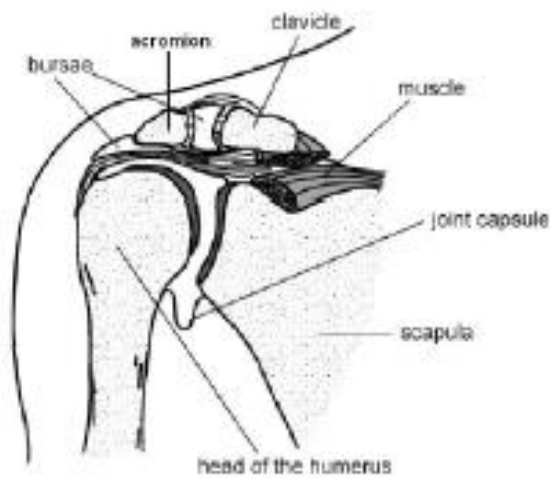
	<b>Left</b>		<b>Right</b>	
Neer Impingement sign	+ve / -ve		+ve / -ve	
Hawkins and Kennedy test	+ve / -ve		+ve / -ve	
Pain on palpation of gtr tuberosity	Yes / No		Yes / No	
<b>R.O.M</b> active / passive				
Flexion <i>(X° measured with inclinometer)</i>				
Abduction <i>(X° measured with inclinometer)</i>				
ER by side <i>(cm measured with tape measure)</i>				
HBB  <i>(lateral buttock, posterior buttocks, sacrum, lower lumbar, lumbo thoracic region, lower thoracic, inferior angle scapula, middle scapula, superior angle scapula) - write level</i>				

<b>Resisted mvts. &amp; Strength</b>	<b>Left</b>	<b>Right</b>
Abduction 10° ( <i>pain, pain and weakness, weakness</i> )		
Flexion 10° ( <i>pain, pain and weakness, weakness</i> )		
Full cans ( <i>pain, pain and weakness, weakness</i> )		
Empty cans ( <i>pain, pain and weakness, weakness</i> )		
ER by side ( <i>pain, pain and weakness, weakness</i> )		
IR by side ( <i>pain, pain and weakness, weakness</i> )		
Biceps ( <i>pain, pain and weakness, weakness</i> )		

**Comments:**

# SHOULDER CLASS

## Patient Information Booklet



THE SHOULDER JOINT

Name.....

Physiotherapy Department

St George's Healthcare **NHS**  
NHS Trust

[www.stgeorges.nhs.uk](http://www.stgeorges.nhs.uk)



## KEY POINTS

### **Anatomy**

- We rely on strong muscles to give us the stability to be able to move our arms freely.
- Shoulder pain is very common because many people experience problems with the muscles and soft tissues of the shoulder.
- This class therefore aims to strengthen the relevant muscles and help reduce your shoulder pain.

### **Pain and Pacing**

- It is important to strengthen your shoulder in a controlled way.
- Therefore, on a scale of 0-10, if 0 is no pain and 10 is the worst pain that you can imagine, your pain should only reach 1-2/10 during or after these exercises.
- If you do experience extra pain, it does not mean that you have caused any damage to your shoulder, it is simply that the muscles are adjusting to the new demands placed on them.
- When exercising, start at a level that you will be able to maintain.

## **KEY POINTS**

### **Role of Investigations**

- Many people will have tears in their shoulder tendons.
- The body naturally compensates for these and they are often not the cause of pain.
- The most reliable information for the diagnosis and treatment for your shoulder is from the clinical examination.

### **Research on Shoulder Rehabilitation**

- Physiotherapy has been shown to be just as effective as surgery for the treatment of shoulder pain.
- There are unlikely to be any adverse effects from physiotherapy.



## **Shoulder Class    Abduction mobilisation**



### **Start**

**With your arm 45° out to the side (see photo)**  
**Lift hand to hold band at a comfortable height**  
**Gently pull the band down and hold your hand by your side**  
**Let the band pull your arm up as slowly as possible**  
**Keep repeating this but avoid pain and fatigue**



### **Progression**

**Gently open the fingers of the hand holding the band**  
**Use your other hand to 'tighten' the band by pulling it towards the floor**  
**Now close your fingers around the band again and let the band lift your arm higher**  
**Use the band to take your arm higher but don't progress if you start to feel pain in your shoulder ... and repeat**

## Shoulder Class Ainsworth programme



### Exercise programme

- Lie down supporting your upper arm on a pillow or towel
- Point your fingers towards the ceiling
- Gently lift your arm off the pillow (*keep point your fingers upwards*)
- Lift your arm as high as you are able, hold for a few seconds if you can and then lower your arm back to the pillow (*keep your fingers pointing up*)
- Repeat as many times as you can (initially this may only be a few times but with time you should be able to progress)
- Don't push into pain and if you get tired rest your arm



- If you are finding the exercise very difficult you can use your other arm to help (3-4)
- Try and use your other arm only to help through the range that you are finding difficult (this may be at the beginning, or the middle or the end of the movement) (3-4)
- Holding a small weight (eg small bottle of water) sometimes may help (5)



## Shoulder Class    Ainsworth programme



### Progression

When you can hold your arm up you can progress this exercise

Slowly and gently move your arm backwards and forwards (*as in the photos*)

This will help to build up your shoulder strength and control

Only do a few to start with, avoiding pain and fatigue

Lower your arm by bending the elbow and keep your fingers facing towards the ceiling

*....repeat*

## Shoulder Class    Ainsworth programme

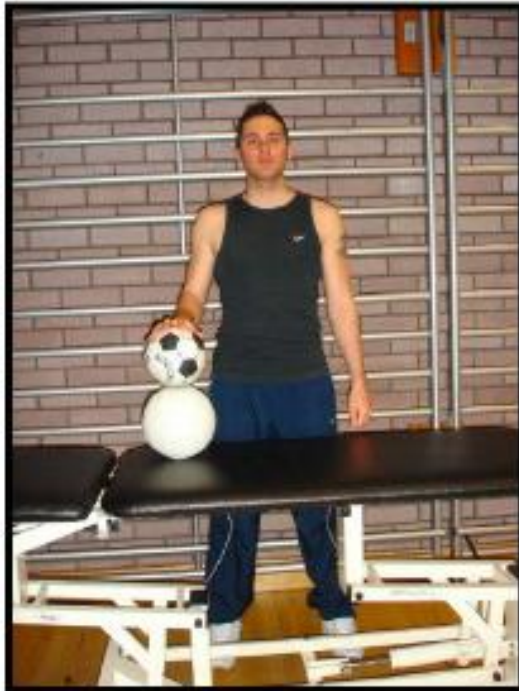


- Progress by sitting up a little higher
- Make sure you keep your fingers pointing at the ceiling
- You can use your other hand to help
- You can use a small weight to help lift up your arm
- Repeat as many times as you can (initially this may only be a few times but with time you should be able to progress)
- Don't push into pain and if you get tired rest your arm



- Finally try the exercises in sitting and standing
- Go through the same progression of the exercises
- You may find them easier if you use your other arm for some support and help when needed
- You can also try a small weight

## Shoulder Class



## Balancing balls

### Exercise 1

**Balance 2 balls on a table**

**Try and balance them with your eyes closed**

**Try and balance the balls and move side to side**



### Exercise 2

**Balance 2 large balls**

**Try and balance them with your eyes closed**

**Try and take a step forwards and backwards whilst balancing the balls**



## **Shoulder Class   Weight bearing exercises**



### **Exercise 1**

**Take body weight  
through arms**

**The amount of weight  
you take depends on  
your comfort**

**While taking weight  
gently move your body  
side to side and  
backwards and  
forwards**



### **Exercise 2**

**Do press ups against  
a wall**

**Try and progress by  
straightening your  
arms as far as you  
can**

**Slowly lower yourself  
back to the starting  
position**

## Shoulder Class



## External rotation

### Exercise 1

Stand in a comfortable posture

Keep elbow away from side of body

Stretch band by taking hand away from side of body

Make sure you keep your elbow position slightly away from your side



### Exercise 2

Progress by placing opposite foot in front

With band attached at varying heights (from hip to shoulder height and above) stretch band by rotating shoulder away from wall

Only perform at a height that is comfortable for your shoulder

Keep elbow position constant

## Shoulder Class    Flexion mobilisation



### Start

**With your arm out in front (see photo)**

**Lift hand to hold band at a comfortable height**

**Gently pull the band down and hold your hand by your side**

**Let the band pull your arm up as slowly as possible**

**Keep repeating this but avoid pain and fatigue**



### Progression

**Gently open the fingers of the hand holding the band**

**Use your other hand to 'tighten' the band by pulling it towards the floor**

**Now close your fingers around the band again and let the band lift your arm higher**

**Use the band to take your arm higher but don't progress if you start to feel pain in your shoulder ....and repeat**



## **Shoulder Class    Forward arm raises**



### **Exercise 1**

**Stand with right leg forwards**

**Shift body weight forwards onto right leg**

**At the same time swing left arm forwards**

**Repeat with opposite leg and arm**



### **Exercise 2**

**Progress by using a band secured at floor level**

**Perform the same exercise**

**Stretching the band as you move your arm forwards**

## Shoulder Class

## Internal rotation



### Exercise 1

Stand in a comfortable posture

Keep elbow gently by side of body

Stretch band by taking hand across your body

Hold and slowly return



### Exercise 2

Place opposite foot in front

Progress by taking arm out to side

Start close to side and then progress so that arm is parallel with the floor

Stretch band by taking hand forwards (rotating at the shoulder)

Hold and slowly return

## Shoulder Class "Rolling a ball"



### Exercise 1

**Imagine holding a small ball**

**Roll hands around the ball**

**As you 'roll the ball' move your hips in the opposite direction**



### Exercise 2

**Imagine holding a larger ball**

**Roll hands around the ball**

**As you 'roll the ball' move your hips in the opposite direction**



## **Shoulder Class    Shoulder blade exercises**



### **Exercise 1**

**Sitting with your hands on your hips**

**Slowly move your shoulders up and down**

**Then forwards and backwards**

**Once you have done this hold in each position for a few seconds**



### **Exercise 2**

**Now try and do the same exercise while sitting on a ball**

## Shoulder Class    Shoulder repositioning



### Exercise 1

**Point at an object**  
*(make sure it is in a position that does not cause an increase in your shoulder pain)*

**While pointing at the object close your eyes**

**Keep your eyes closed and now place your hand by your side**

**Point back at the object and now open your eyes**

***Are you pointing at the same object?***



### Exercise 2

**Repeat the same exercise**

**While your eyes are closed make small circles around the object.**

**After 10-20 seconds open your eyes.**

***Are you still pointing at the same object?***

**Your circles can be in both clockwise and anti-clockwise directions**



## Shoulder Class    Shoulder retraction



### **Start**

**With your arms elevated to 90° and with your elbows and forearms in front of you**

***Make sure your thumbs face away from the wall***



### **Progression**

***Retract your shoulders by gently squeezing your shoulder blades together***

**Hold for a few seconds and slowly release**

***...repeat***

## **Shoulder Class**

## **Walking on the spot**



### **Exercise 1**

**Walk on the spot**

**Gently swing your  
arms backwards  
and forwards**



### **Exercise 2**

**Walk on the spot**

**Step as high as you  
can and swing your  
arms backwards  
and forwards as  
high as you are  
able**

**If you can progress  
to a jog**

**Contact Details:**

St Georges Hospital  
Blackshaw Road  
Tooting  
London  
SW17 0QT  
Phone: 0208 672 1255

---

## Study diary

These were in A4 format for the participants.

<b>Guy's and St Thomas'</b> NHS Foundation Trust		<b>St Thomas' Hospital</b> Physiotherapy Department Third Floor Lambeth Wing St Thomas' Hospital Lambeth Palace Road London SE1 7EH Tel: 020 7188 4174 Email: <a href="mailto:Fiona.sandford@kcl.ac.uk">Fiona.sandford@kcl.ac.uk</a>
---	--	---

**Participants Exercise and Tablet Diary**  
 Version 1 Date 04.04.08

Local Research Ethics Number: 08/H0805/21

Patient Hospital Number:

Patient Study Identification Number:

Patient Initials:

	Date	No of tablets taken?	Form of Exercise session undertaken each day		Comments. Please fill in any extra comments in the space provided.
			Shoulder exercise group (Y/N)	Shoulder exercise session at home (hrs:mins)	
<b>Week 1</b>					

- 1 -

100 words

<b>Guy's and St Thomas'</b> NHS Foundation Trust	
---	--

**St Thomas' Hospital**  
 Physiotherapy Department  
 Third Floor Lambeth Wing  
 St Thomas' Hospital  
 Lambeth Palace Road  
 London SE1 7EH  
 Tel: 020 7188 4174  
 Email: [Fiona.sandford@kcl.ac.uk](mailto:Fiona.sandford@kcl.ac.uk)

	Date	No of tablets taken?	Form of Exercise session undertaken each day		Comments. Please fill in any extra comments in the space provided.
			Shoulder exercise group (Y/N)	Shoulder exercise session at home (hrs:mins)	
<b>Week 1 cont</b>					

- 2 -

100 words

### Baseline outcome measures in each treatment group

The outcome measures were compared and analysed at baseline including the primary outcome measure the oxford shoulder score and all secondary outcome measures. Significant differences were observed in baseline measures of the SF 36 mental component scores (p=0.02) and SF36 role limitations due to emotional problems (p=0.04).

Table 11.1 Baseline outcome measures

Domain	Outcome measure	Placebo	Treatment	P value
Function	Oxford shoulder score (OSS)	31.71 (8.41)	32.03 (7.85)	0.87
	0-48 48=highest			
	SPADI, 0-100; 100=highest	43.92	38.85	0.20
		(29.39-58.46)	(20.13-55.02)	
	Patient specific functional scale, 0-100; 100=highest	33.33	35.00	0.90
		(26.67-50)	(20.00-50.83)	
Pain	Pain score (NRS)	6.26 (1.83)	5.99 (0.26)	0.57
	0-10; 0=highest			
Quality of life- generic	EQ-5D utility score	0.68 (0.23)	0.70 (0.26)	0.75
	-0.5-1.0; 1=highest			
	EQ-5D health quality VAS	74.92 (13.59)	70.24 (19.39)	0.47
Quality of life- specific	0-100; 100=highest			
	SF36 MCS	54.67 (8.03)	49.64 (10.13)	0.02*
	0-100; 100=highest			
	SF36 PCS	37.95 (8.18)	41.54 (8.26)	0.07
	0-100; 100=highest			
	Sf36 physical role	25 (0-75)	50 (0-100))	0.51
	SF36 physical functioning	65.86 (20.77)	68.16 (23.20)	0.66
	SF36 bodily pain	47.89 (19.07)	51.61 (21.70)	0.44
	SF36 general health	67.80 (15.44)	70.03 (19.89)	0.60
	SF36 vitality	60.57 (6.54)	60.57 (18.14)	1.00

	SF36 social functioning	78.86 (22.09)	73.36 (22.36)	0.39
	SF36 role limitations due to emotional problems	80.95 (35.51)	61.40 (44.88)	0.04*
	SF36 mental health	79.94 (15.13)	78.38 (14.75)	0.30
Impairment measures- ROM	Gh jt flexion (degrees)	141.11 920.89)	140.37 (18.25)	0.87
	Gh jt abduction (degrees)	134.60 (28.38)	131.47 (27.93)	0.64
	Gh jt external rotation (degrees)	41.08 (5.73)	39.29 (6.12)	0.20
	Hand behind back (cm)	31.03 (10.13)	30.79 (12.20)	0.93
Impairment measures- Strength (measured in pounds)	Gh jt flexion	21.59 (6.09)	21.13 (9.65)	0.82
	Gh jt abduction	21.62 (8.99)	19.33 (8.46)	0.27
	‘Full can’	9.50 (5.20-120)	6.35 (4.65-12.1)	0.26 $\bar{T}$
	‘Empty can’	9.20 (5.20-12.20)	6.35 (3.78-10.18)	0.10 $\bar{T}$
	External rotation	16.20 (9.70-21.30)	12.45 (9.10-16.08)	0.09 $\bar{T}$
	Internal rotation	18.30 (13.00-25.50)	15.85 (11.45-23.35)	0.25 $\bar{T}$
	Elbow flexion	23.50 (17-33.50)	22.60 (12.50-33.10)	0.61 $\bar{T}$

Summary measures represent means (SD), independent t-test or  $\bar{T}$  represents Mann Whitney and median (interquartile ranges). \*represents a statistically significant difference. Gh jt= gleno humeral joint, MCS= mental component score (SF36), PCS= physical component score (SF36)

## Baseline characteristics of those completing the trial and those who did not

Baseline characteristics of those participants completing and not completing are presented in Table 11.2.

For those not completing the longevity outcome at one year:

The baseline disability as measured by Oxford Shoulder Score (OSS), was significantly more severe in non-completers (26, SD =8.07) compared to those who completed the trial (32.6 SD=7.8,  $t(71)=2.25$ ,  $p=0.03$ , 95%CI= 0.74 to 12.46). Similarly the baseline SPADI score for the non completers (61.27±18.98) showed significantly higher levels of disability than the completers (38.32±20.97,  $p=0.004$ , 95%CI=-38.47 to -7.42). All baseline health related quality of life scores were statistically significantly lower in the non-completer group EQD5-3L ( $p=0.0001$ , 95% CI=0.17 to 0.50), EQD5- VAS score ( $p=0.0004$ , 95% CI=9.91 to 32.27) and the SF-36 PCS and MCS ( $p=0.0008$ , 95%CI =4.36 to 15.98 and  $p=0.025$ , 95%CI=1.01 to 14.75) respectively. With regards to the impairment measures, there was only a statistically significant difference in the range of motion of flexion ( $p=0.004$ , 95%CI of the difference=6.98 to 34.52), abduction ( $p=0.03$ , 95%CI of the difference=2.95 to 43.60) and hand behind back ( $p=0.05$ , 95%CI of the difference=-16.49 to -0.14) all displaying a significantly lower range in those who did not complete the trial. Finally the baseline EPA + DHA levels in the non-completers plasma was statistically significantly higher in the non-completers group ( $p=0.02$ , 95% CI of the difference =-3.08 to -0.73).

Table 11.2 Baseline characteristics of participants that did and did not complete the trial at one year

Domain	Variable/ outcome measure	Participants completing the trial (N=65)	Participants not completing the trial (N=8)	P value
Demographics	Allocated to treatment group	33/65 (50.8%)	5/8 (62.5%)	0.76‡
	Gender: male	33/65 (50.7%)	4/8 (50%)	1.0‡
	Age (years)	52.91 (14.43)	45.88 (8.98)	0.18
	Body mass index (kgm <sup>-2</sup> )	27.58 (6.96)	32.38 (4.84)	0.06
	Waist circumference (cm)	96.03(14.86)	102.43 (12.64)	0.25
	Baseline EPA & DHA plasma levels (%)	3.17 (1.30)	5.07 (2.78)	0.002*
	Symptom duration (months)	21.30 (38.56)	28.69 (38.33)	0.43†
	Analgesia: yes	11/65 (16.9%)	2/8 (25%)	0.64‡
Function	Oxford Shoulder Score (OSS) (0-48; 48= highest)	32.60 (7.82)	26.00 (8.07)	0.03*
	SPADI (0-100; 100=highest)	38.32 (20.97)	61.27 (18.98)	0.004*
	Patient specific functional score (0-100; 100=highest)	37.85 (20.00)	35 (20.93)	0.97†
Pain	Pain score (NRS) (0-10; 0=highest)	6.01 (2.05)	7.00 (1.07)	0.19



Quality of life - generic	Quality of life (EQ-5D) (-0.5-1.0; 1=highest)	0.73 (0.18)	0.39 (0.43)	0.03*‡
	Health quality EQ -5D (0-100; 100=highest)	74.84 (15.51)	53.25 (16.57)	0.0004*
Quality of life – specific SF36 (0-100; 100=highest)	Physical role	51.92 (38.86)	3.13 (8.84)	0.008*‡ (95%CI=21.16-76.44)
	Physical functioning	69.38 (21.17)	48.13 (19.99)	0.009* (5.53-36.98)
	Bodily pain	52.45 (19.23)	28.50 (18.02)	0.03*‡ (95%CI=9.67-38.23)
	General health perceptions	70.80 (16.80)	54.00 (19.84)	0.011* (95%CI=4.00-29.60)
	Vitality	60.80 (13.32)	58.75 (19.96)	0.70
	Social functioning	78.65 (20.46)	50.00 (20.04)	0.00* (95%CI=13.40-43.91)
	Role limitations due to emotional problems	77.44 (37.32)	16.66 (35.63)	0.00*‡ (95%CI=(33.01-88.53)

	Mental health	76.31 (19.96)	72.00 (21.59)	0.49
	Physical component summary	40.93 (8.05)	30.76 (4.62)	0.0008*
	Mental component summary	52.92 (9.12)	45.04 (9.85)	0.025*
Impairment measures-ROM (degrees)	Flexion	143.0 (16.0)	122.25 (33.42)	0.004*
	Abduction	135.52 (25.71)	112.25 (38.22)	0.025*
	External rotation	40.45 (6.03)	37.75 (5.04)	0.23
	Hand behind back	30.0 (10.61)	38.31 (13.64)	0.046*
Impairment measures- Strength (pounds)	Flexion	21.96 (7.72)	16.04 (9.67)	0.53
	Abduction	21.07 (8.65)	15.23 (8.14)	0.195†
	Full can	8.86 (5.52)	8.70 (6.79)	0.84†
	Empty can	8.59 (4.90)	5.56 (4.51)	0.15†
	External rotation	14.30 (6.24)	11.64 (6.63)	0.15†
	Internal rotation	18.45 (7.95)	14.31 (9.01)	0.18
	Elbow flexion	26.60 (14.48)	20.48 (18.08)	0.28

Legend; N= number, CI= 95% confidence interval of the difference. Summary measures are means and (SD) between group comparison analysed using independent samples t test or †denotes Chi squared test, ‡= Fischer's Exact test and †Mann Whitney.

### SF 36 domains across all time points for both groups

Domain	Time point	Placebo	Treatment	Treatment effect (95% CI)	P value	ANCOVA
Physical role	Baseline	N=35 42.86 (38.14)	N=38 50.00(41.51)		0.45	
	2 months	N=32 70.31(31.39)	N=36 62.28 (40.65)	5.03(-12.72-22.79)	0.57	0.57
	3 months	N=31 66.94 (37.30)	N=31 75.81(35.05)	-8.87(-27.26-9.52)	0.34	0.78
	6 months	N=30 75.00 (27.85)	N=32 70.31 (40.88)	4.69(-13.20-22.58)	0.60	0.65
	12 months	N= 32 78.13 (32.84)	N= 32 75.00(39.14)	3.13(21.18-21.19)	0.73	0.31
Physical functioning	Baseline	N=35 65.86 (20.77)	N=38 68.16 (23.20)		0.66	
	2 months	N=32 76.72 (19.90)	N=36 78.47 (19.00)	-1.75 (-11.18-7.67)	0.71	0.65
	3 months	N=31 74.19 (20.86)	N=31 83.23(15.84)	-9.03(-18.44-0.38)	0.06	0.14
	6 months	N=30 77.50 (18.65)	N=32 84.84 (12.15)	-7.34(-15.29-0.60)	0.07	0.029*(0.012 to 0.38)
	12 months	N= 32 79.38 (19.71)	N= 32 79.69(23.35)	-0.31 (-11.11-10.48)	0.95	0.77
Bodily pain	Baseline	N=35 47.89 (19.07)	N=38 51.61 (21.70)		0.44	
	2 months	N=32 64.66 (19.72)	N=36 67.31 (18.09)	-2.65 (-11.81 to 6.51)	0.57	0.67

	3 months	N=31 62.23 (20.29)	N=31 71.06 (19.09)	-8.84 (-18.85 to 1.17)	0.08	0.12
	6 months	N=30 73.37 (18.25)	N=32 74.47 (21.46)	--2.10 (-11.26 to 9.05)	0.83	0.53
	12 months	N= 32 69.63 (22.20)	N= 32 80.22 (19.39)	-10.59 (-21.02 to -0.18)	0.05*	0.04*(-0.105 to 0.479)
General health perceptions	Baseline	N=35 67.80 (15.44)	N=38 70.03 (19.89)		0.60	
	2 months	N=32 70.09 (16.66)	N=36 74.64 (19.20)	-4.55 (-13.30-4.21)	0.30	0.21
	3 months	N=31 69.61 (16.68)	N=31 74.19(19.90)	-4.58(13.91-4.75)	0.33	0.72
	6 months	N=30 72.20 (11.46)	N=32 75.69 (17.35)	-3.49(-11.01-4.03)	0.36	0.56
	12 months	N= 32 70.72 (16.66)	N= 32 71.88(20.47)	-1.16(-10.48-8.17)	0.81	0.70
Vitality	Baseline	N=35 60.57 (6.54)	N=38 60.57 (18.14)		1.00	
	2 months	N=32 63.75 (14.26)	N=36 64.31 (16.87)	-0.56 (-8.17-7.06)	0.89	0.62
	3 months	N=31 65.97(13.57)	N=31 64.35(17.31)	1.61(-6.29-9.51)	0.68	0.96
	6 months	N=30 67.50 (14.78)	N=32 64.84 (16.78)	2.66(-5.40-10.71)	0.51	0.94
	12 months	N= 32 65.78 (16.71)	N= 32 62.81(18.45)	2.97 (-5.83-11.76)	0.50	0.98
Social functioning	Baseline	N=35 78.86 (22.09)	N=38 73.36 (22.36)		0.39	
	2 months	N=32 84.38 (20.58)	N=36 81.25 (20.16)	3.13(-6.75-13.00)	0.53	0.90

	3 months	N=31 82.66(24.08)	N=31 85.08(18.94)	(-13.43-8.59)	0.66	0.60
	6 months	N=30 89.58 (13.16)	N=32 84.77 (19.76)	4.82(-3.77-13.41)	0.27	0.56
	12 months	N= 32 85.55 (18.81)	N= 32 84.37(23.55)	1.17 (-9.48-11.82)	0.83	0.74
Role limitations due to emotional problems	Baseline	N=35 80.95 (35.51)	N=38 61.40 (44.88)		0.04*	
	2 months	N=32 77.08 (35.36)	N=36 74.07 (39.93)	3.01 (-15.35 to 21.37)	0.75	0.64
	3 months	N=31 88.18 (23.64)	N=31 86.02 (29.53)	2.15 (-11.44 to 15.75)	0.75	0.65
	6 months	N=30 87.78 (23.95)	N=32 76.04 (35.15)	11.74 (-3.65 to 27.12)	0.13	0.64
	12 months	N= 32 86.46 (29.16)	N= 32 77.08 (35.36)	9.38 (-6.82 to 25.57)	0.25	0.47
Mental health	Baseline	N=35 74.94 (15.13)	N=38 78.38 (14.75)		0.30	
	2 months	N=32 78.38 (14.75)	N=36 75.89 (16.27)	2.49 (-5.07 to 10.04)	0.51	0.96
	3 months	N=31 82.55 (10.93)	N=31 79.68 (14.93)	2.87 (-3.78 to 9.52)	0.39	0.85
	6 months	N=30 78.13 (11.00)	N=32 78.03 (15.62)	0.10 (-6.80 to 7.01)	0.98	0.72
	12 months	N= 32 76.38 (14.20)	N= 32 76.88 (16.47)	-0.50 (-8.18 to 7.18)	0.90	0.24

Summary measures are means and (SD) analysed using independent samples t test and between group comparison by univariate ANCOVA adjusted for baseline value, age, gender and BMI. Scores are an aggregate percentage where 0= worst possible functioning and 100=best. \*signifies a statistically significant change.

### Shoulder range of motion across all time points for both groups

Outcome measure	time point	Placebo	Treatment	P value	ANCOVA
Symptomatic GHJ flexion (measured in degrees)	Baseline	141.11 (20.89)	140.37 (18.25)	0.87	
	2 months	144.52 (19.35)	145.24 (18.99)	0.87	0.45
	3 months	146.61 (13.40)	152.77 (11.80)	0.06	0.005*
	6 months	150.57 (16.00)	151.09 (16.62)	0.9	0.45
	12 months	149.69 (13.77)	151.65 (17.20)	0.62	0.36
Symptomatic GHJ abduction (measured in degrees)	Baseline	134.60 (28.38)	131.47 (27.93)	0.64	
	2 months	144.27 (20.32)	138.11 (24.33)	0.26	0.49
	3 months	140.39 (20.32)	148.36 (12.42)	0.05*	0.006*
	6 months	149.20 (17.59)	148.13 (17.39)	0.81	0.86
	12 months	146.13 (18.50)	150.84 (16.24)	0.29	0.11
Symptomatic GHJ external rotation (measured in cm)	Baseline	41.08 (5.73)	39.29 (6.12)	0.20	
	2 months	41.36 (5.90)	40.54 (4.93)	0.53	0.69
	3 months	42.02 (6.89)	41.92 (5.60)	0.95	0.08
	6 months	42.41 (6.35)	40.56 (7.18)	0.28	0.10
	12 months	43.98 (5.73)	42.36 (5.51)	0.26	0.90
Symptomatic	Baseline	31.03	30.79 (12.20)	0.93	

GHJ hand behind back (measured in cm)		(10.13)			
	2 months	28.26 (10.17)	28.63 (10.40)	0.88	0.79
	3 months	27.53 (10.22)	25.78 (9.15)	0.49	0.41
	6 months	26.15 (7.75)	24.59 (6.46)	0.39	0.43
	12 months	24.83 (10.28)	23.38 (7.49)	0.54	0.60

### Shoulder strength across all time points for both groups.

Outcome measure	Assessment time point	Placebo	Treatment	P value	ANCOVA
Symptomatic GHJ flexion (measured in pounds)	Baseline	21.59 (6.09)	21.13 (9.65)	0.82	
	2 months	24.52 (7.07)	22.76 (10.45)	0.42	0.89
	3 months	25.20 (7.55)	22.09 (10.34)	0.18	0.64
	6 months	27.06 (7.41)	26.39 (11.27)	0.76	0.44
	12 months	26.62 (8.68)	25.57 (9.86)	0.66	0.26
Symptomatic GHJ abduction (measured in pounds)	Baseline	21.62 (8.99)	19.33 (8.46)	0.27	
	2 months	25.70 (8.71)	22.42 (9.88)	0.15	0.71
	3 months	25.55 (9.55)	22.28 (9.68)	0.19	0.90
	6 months	26.70 (7.16)	24.85 (9.44)	0.39	0.63
	12 months	27.58 (7.54)	27.15 (10.14)	0.85	0.13
Symptomatic full can strength (measured in pounds)	Baseline	9.40 (5.42)	8.33 (5.83)	0.42	
	2 months	11.43 (5.97)	10.23 (7.46)	0.45	0.92
	3 months	12.23 (6.54)	10.82 (7.59)	0.44	0.27
	6 months	12.37 (5.89)	11.69 (7.12)	0.69	0.35
	12 months	13.04 (5.14)	12.56 (7.04)	0.76	0.15
Symptomatic empty can strength (measured in pounds)	Baseline	9.13 (4.44)	7.46 (5.26)	0.15	
	2 months	11.78 (5.51)	10.31 (6.91)	0.33	0.60
	3 months	12.64 (5.43)	9.88 (6.58)	0.007	0.61
	6 months	13.10 (5.10)	11.53 (6.50)	0.30	0.16
	12 months	14.25 (7.99)	12.78 (6.53)	0.43	0.48
Symptomatic external rotation strength (measured in pounds)	Baseline	15.44 (6.28)	12.70 (6.08)	0.06	
	2 months	16.78 (5.75)	15.55 (7.58)	0.45	0.59
	3 months	17.75 (6.62)	16.23 (7.55)	0.40	0.22
	6 months	18.74 (5.75)	16.74 (6.91)	0.2	0.68



	12 months	17.75 (5.53)	18.69 (7.15)	0.56	0.005*
Symptomatic internal rotation strength (measured in pounds)	Baseline	19.17 (8.11)	16.91 (8.07)	0.24	
	2 months	22.13 (8.88)	19.10 (9.79)	0.18	0.90
	3 months	23.83 (9.88)	21.38 (10.95)	0.36	0.55
	6 months	24.32 (9.75)	20.67 (10.48)	0.16	0.63
	12 months	24.55 (9.06)	23.07 (10.93)	0.56	0.60
Symptomatic elbow flexion strength (measured in pounds)	Baseline	26.72 (14.86)	25.19 (15.09)	0.67	
	2 months	31.28 (13.46)	29.44 (16.26)	0.61	0.61
	3 months	32.90 (15.44)	30.27 (17.57)	0.53	0.78
	6 months	32.63 (13.05)	33.00 (16.10)	0.92	0.21
	12 months	33.26 (17.05)	31.68 (15.69)	0.71	0.59

## Ethical approval for qualitative study



**NRES Committee London - Bromley**

Bristol Research Ethics Committee Centre  
Whitefriars  
Level 3, Block B  
Lewins Mead  
Bristol  
BS1 2NT

Tel: 0117 342 1387  
Fax: 0117 342 0445

12 September 2012

Dr Jeremy Lewis  
Research Lead  
Chelsea and Westminster Hospital NHS Foundation Trust  
Therapy Department  
Chelsea and Westminster Hospital  
369 Fulham Road, London  
SW10 9NH

Dear Dr Lewis

**Study title:** RANDOMISED SINGLE-BLINDED PLACEBO-  
CONTROLLED STUDY INVESTIGATING THE ROLE OF  
POLY-UNSATURATED FATTY ACIDS IN ADDITION TO  
EXERCISE IN THE MANAGEMENT OF ROTATOR CUFF  
(RC) TENDINOPATHY.  
**REC reference:** 08/H0805/21  
**Amendment number:** Amendment 3: 8th August 2012  
**Amendment date:** 08 August 2012

The above amendment was reviewed by the Sub-Committee in correspondence.

### Ethical opinion

There were no ethical issues.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

### Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
CV - Fiona Sandford	4	25 July 2012
Participant Information Sheet	2	04 September 2012
Protocol	1	25 July 2012

A Research Ethics Committee established by the Health Research Authority

Notice of Substantial Amendment (non-CTIMPs)	Amendment 3: 8th August 2012	08 August 2012
Covering Letter		25 July 2012
Participant Consent Form	2	11 September 2012

#### **Membership of the Committee**

The members of the Committee who took part in the review are listed on the attached sheet.

#### **R&D approval**

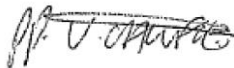
All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

#### **Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

<b>08/H0805/21:</b>	<b>Please quote this number on all correspondence</b>
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Yours sincerely



**Ms Carol Jones**  
**Chair**

E-mail: ubh-tr.BromleyREC@nhs.net

*Enclosures:*                      *List of names and professions of members who took part in the review*

*Copy to:*                          *Dr Kate Blake, Guys and St Thomas' NHS Trust*  
   *Dr Fiona Sandford*

## **Participant information sheet for qualitative study**

### **INFORMATION SHEET FOR PARTICIPANTS**

*REC Reference Number: 08/H0805/21*

**YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET**

**Factors affecting compliance to exercise program and supplement use in the management of rotator cuff tendinopathy.**

Thank you for your recent participation in the randomized single-blinded placebo controlled study investigating the role of poly-unsaturated fatty acids in addition to exercise in the management of Rotator cuff tendinopathy.

We would now like to invite you to participate further in this study, if you would like to. You should only participate if you want to; choosing not to take part will not disadvantage you in any way.

Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

#### **What is the purpose of the research study?**

We would like to hear about your experiences while doing the exercises and taking the supplements during the study, including things that helped you to carry out the exercises and take the nine pills and things that made it difficult to follow. The purpose of the research study is to explore the factors affecting compliance or adherence to carrying out prescribed exercises and to taking supplements. The findings will benefit health professionals and public health practitioners in their roles supporting individuals to carry out physiotherapy exercises and take supplements to treat musculo-skeletal pain such as rotator cuff tendinopathy.

#### **Why am I being invited to take part?**

You have been invited to take part in this study because you recently took part in study.

You are well-placed to discuss your experiences of taking the pills and doing the exercises, and provide insights into how it felt.

**Do I have to take part?**

No. It is up to you to decide whether or not to take further part in this study. If you choose to participate you are free to withdraw at any time without giving a reason and without your decision impacting in any way on your future interaction with the researchers from study or Guys and St Thomas' NHS Foundation Trust.

**What would be involved?**

You may be asked to attend an individual interview either on a separate occasion or as part of your final assessment in the study with the chief investigator and clinical specialist physiotherapist, Fiona Sandford. The agenda will be flexible so that you can raise anything of particular relevance or importance to you.

Interviews will last up to one hour and will be recorded on a tape recorder and by pen and paper, transcribed into print and then analysed. The discussion will focus on your experiences of taking part in the study.

You will be reimbursed for your travel expenses up to the value of an off peak one day zone 1-4 travel card on provision of a receipt.

**Will I be identifiable in the transcription of the interview or in any subsequent verbal or written report?**

No. Participation in the interview is completely confidential and all information you provide will be anonymised. You will not be personally identifiable in the typed transcription (you will be given a pseudonym) or in any subsequent verbal or written account. The tapes will not be heard by anyone other than the researcher and neither your name nor your place of work will appear in the printed copy.

Once transcribed, the tape recording will be permanently deleted. You will be offered a copy of the transcript of the interview, if you wish to receive it. Nothing discussed during the interview or focus group will be divulged to a third party outside of the research team and only the research team will have access to the transcripts from the study. Where direct quoting is used in any report or publication, these will be anonymised and will be chosen in order to prevent them from being linked with any individual. The results of the study will eventually be published. You will be offered a summary of the final research report once it has been published.

**How quickly must I decide if I want to participate?**

A researcher will be in contact with you in the next two weeks to answer any questions you might have and to ask if you are willing to participate and, if you are willing, to arrange a time convenient for you to attend the interview.

It is up to you to decide whether to take part or not. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You are free to refuse to discuss specific questions during the interview should you wish, without giving a reason. You are also free to withdraw from the study at any time prior to data analysis, without giving a reason, and any data collected by that point will not be used in the analysis. Once data analysis is underway it will not be possible to withdraw your data, as by this stage it will be anonymised.

**What are the possible benefits of taking part?**

Although you are unlikely to obtain any individual benefit from participating further in the study, the results will be of benefit to health care practitioners, future research projects and public health policy makers in the area of rotator cuff tendinopathy, physiotherapy and supplementation.

**What are the potential risks or disadvantages of taking part?**

There are unlikely to be any risks or disadvantages to you by taking part.

If you have any questions or would like to discuss this in more detail then please contact the investigator:

Fiona Sandford, Chief investigator and clinical Specialist Physiotherapist email:  
Fiona.sandford@kcl.ac.uk or 07836622076

**What will happen if anything goes wrong?**

We do not anticipate for anything to go wrong in this study. If you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms are available to you.

**Thank you for taking the time to read this and your interest in the study.**

Consent form for qualitative study

**Guy's and St Thomas'**  
NHS Foundation Trust



**Research Subject Consent Form**

**St Thomas' Hospital**  
Physiotherapy Department  
Third Floor Lambeth Wing  
St Thomas' Hospital  
Lambeth Palace Road  
London SE1 7EH  
Tel: 020 7188 4174  
Fax: 020 7188 4166

**Title of Project:** Factors affecting compliance to exercise program and supplement use in the management of rotator cuff tendinopathy

Protocol Version: Version 1 date: 25.07.2012

Local Research Ethics Number: 08/H0805/21

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**Participant Declaration**

**If Correct**

**Please initial box**

I have been given the chance to read and understand the information sheet (dated 05.09.2012 version2) relating to the above study

I have been given the opportunity to ask questions and discuss the study.

I have been made aware of the risks/ benefits

I understand that authorised individuals may look at my medical notes and give permission for these individuals to have access

I understand that I am free to withdraw from this study at any time without prejudice to my future care/ treatment



I consent to audio taping of the interview/discussion

☐

I would like to receive a one page summary of the findings of this study.

☐

**Title of Project: Factors affecting compliance to exercise program and supplement use in the management of rotator cuff tendinopathy**

Protocol Version: Version 1 date: 25.07.2012

Local Research Ethics Number: 08/H0805/21

Patient Hospital Number:

I agree to take part in the above study

Signature .....

Name .....

Date .....

**Person responsible for obtaining Informed Consent:**

'To the best of my knowledge I have provided the above individual with sufficient information to enable them to give informed consent'.

Signature .....

Name .....

Date .....

Position .....

**Witnessed by:**

Signature .....

Name .....

Date .....

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## Rotator Cuff Tendinopathy: Is There a Role for Polyunsaturated Fatty Acids and Antioxidants?

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**ABSTRACT:** Despite the lack of robust evidence, there has been a steady increase in the use of dietary supplements, including Omega 3 fatty acids and antioxidants, in the management of musculoskeletal conditions. One reason for this is that unsatisfactory outcomes with conventional treatments have lead sufferers to seek alternative solutions including the use of nutritional supplements. In the United Kingdom alone, the current supplement market is estimated to be over £300 million per annum. One target market for nutritional supplements is tendinopathies including conditions involving the rotator cuff. This condition is debilitating and associated with considerable morbidity. Incidence increases with advancing age. High levels of cytokines, such as the pro-inflammatory interleukin 1 $\beta$  and vascular endothelial growth factor, have been reported within the bursa of patients with rotator cuff disease. There is also evidence that high concentrations of free-radical oxidants may also be involved in tendon pathology. Therefore, the possibility exists that dietary supplements may have a beneficial effect on tendon pathology, including that of the rotator cuff. A review was conducted to synthesize the available research literature on the histopathology of rotator cuff disease and the effectiveness of polyunsaturated fatty acids (PUFAs) and antioxidants on tendinopathies. A search was conducted using the MEDLINE, CINAHL, AMED, EMBASE, Cochrane, and PEDro databases using the terms "rotator cuff" and "tear/s" and "subacromial impingement syndrome," "bursae," "bursitis," "tendinopathy," "tendinitis," "tendinosis," "polyunsaturated fatty acids," "PUFA," "Omega 3," "histopathology," "etiology," and "antioxidants." English language was an inclusion criterion. There were no randomized clinical trials found relating specifically to the rotator cuff. Only one trial was found that investigated the efficacy of PUFAs and antioxidants on tendinopathies. The findings suggest that some (low level) evidence exists to support the supplementation in the management of tendinopathies. Any conclusions based on this one article should be reached with caution. Subsequently, there is a distinct and clear need for well-planned randomized controlled trials that aim to investigate the efficacy of supplements in the management of tendinopathies including those of the rotator cuff.

J HAND THER. 2009;22:49–56.

### BACKGROUND

It is estimated that 40% of U.K. adults regularly use dietary supplements, thereby making the annual U.K. market alone worth over £300 million.<sup>1</sup> Similarly, up to 52% of adults in the U.S. report taking a dietary supplement.<sup>2</sup> Despite this widespread utilization, their use is still controversial with a paucity of

well-conducted research to inform patients and those practitioners within the musculoskeletal fields as to the efficacy of these supplements. Pathology involving the rotator cuff tendons of the shoulder is one of the most common musculoskeletal conditions treated in orthopedic practice. The purpose of this review was to investigate if a rationale exists for the use of supplementation in this condition and then to review the evidence to support or challenge this practice. The principal aim of this review was to synthesize information to help guide clinicians and inform patients regarding the current body of knowledge relating to nutritional supplementation in the management of rotator cuff pathology.

Musculoskeletal disorders of the shoulder are extremely common, with one in three adults experiencing shoulder pain at some stage of their lives.<sup>3</sup> After

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doi:10.1197/j.jht.2008.06.007



lumbar and cervical pathology, shoulder disorders are the most common musculoskeletal condition treated in primary care with between 1.1% and 1.6% of the population attending their general practitioner (GP) annually because of shoulder pain and dysfunction.<sup>4-8</sup> It is estimated that the annual prevalence in the United Kingdom of shoulder pain is 2.36%.<sup>8</sup> The incidence of shoulder pain substantially increases with age, rising to approximately 20% in individuals older than 70 years.<sup>3,8</sup> In addition to the high incidence, shoulder dysfunction is often persistent and recurrent with 54% of sufferers reporting on-going symptoms after three years.<sup>9</sup> It is also associated with substantial morbidity,<sup>10,11</sup> impacting significantly on function with the shoulder being the means of placing the hand.

The high incidence of shoulder pathology has considerable socioeconomic implications due to time lost from work.<sup>12</sup> The estimated annual expenditure to society for shoulder pain is substantial due to health-care costs, social security, and lost production.<sup>6</sup> Disorders of the shoulder contribute 30% of all occupational musculoskeletal pathologies and are equivalent in frequency to disorders of the cervical spine,<sup>13</sup> with an increased prevalence of shoulder pain<sup>14</sup> and with a greater severity of pathology<sup>15</sup> in those working above 90 degrees of shoulder elevation.

## METHODS

A review was conducted to synthesize the available research literature on the histopathology of rotator cuff disease and the effectiveness of polyunsaturated fatty acids (PUFAs) and antioxidants on tendinopathies. A search was conducted using the MEDLINE, CINAHL, AMED, EMBASE, Cochrane, and PEDro databases using the terms "rotator cuff" and "tear/s" and "subacromial impingement syndrome," "burse," "bursitis," "tendinitis," "tendinopathy," "tendinosis," "histopathology," "etiology," "polyunsaturated fatty acids," "PUFA," "Omega 3," and "antioxidants." English language was an inclusion criterion. Only one article was located, which fitted the criteria of the searches.

## DISCUSSION

The majority of shoulder pain is believed to arise from the peri-articular soft tissues, especially the rotator cuff.<sup>16</sup> This view is supported in studies involving industry, primary care, and workers compensation cases, where the most frequent shoulder diagnosis is that of rotator cuff tendinitis, accounting for approximately one thirds of all shoulder diagnoses made by GPs.<sup>5,17</sup> The rotator cuff refers to the group of muscles and tendons that surround the

shoulder joint that work collectively to produce synchronous and precise movement as well as dynamically stabilize the glenohumeral (shoulder) joint. The most superior of these tendons is that of the supraspinatus muscle. Degeneration and tears of the rotator cuff tendons of the shoulder have been strongly correlated with aging.<sup>18-20</sup>

A number of conflicting theories have been proposed to describe the mechanisms causing, and the pathology associated with, rotator cuff disease. Neer<sup>21</sup> (1972) proposed that the main mechanism of rotator cuff disease occurred as a result of irritation to the rotator cuff tendons from the overlying acromion during elevation of the arm leading to tendon tissue irritation and inflammation, hence the term tendinitis. In this model, the site of the irritation is hypothesized to be on the superior or bursal surface of the tendon, which is the aspect of the tendon adjacent to the acromion. Although the acromial irritation theory is appealing and has been widely embraced, the evidence to support it is inadequate and largely equivocal. Findings from cadaver studies have demonstrated that rotator cuff tendon pathology occurs more commonly within the internal substance of the tendon (intrasubstance) or on the undersurface (articular or joint side) of the tendon. These are regions of the tendon not coming in contact with the acromion and to a large extent these findings refute the acromial theory.<sup>22,23</sup>

There is also a lack of evidence to support the tendon inflammation (tendinitis) model. The key cells normally associated with acute inflammation are neutrophils, and the main cells associated with chronic inflammation are macrophages, lymphocytes, and plasma cells. Fukuda et al.<sup>24</sup> (1990) reported no infiltrations or aggregates of neutrophils, lymphocytes, or plasma cells in rotator cuff tendon specimens taken from 12 subjects with rotator cuff disease during surgery, and the term supraspinatus tendinitis or rotator cuff tendonitis appear to be a clinical diagnostic term more than once supported by histological or biochemical evidence.<sup>25,26</sup> However, Matthews et al.<sup>27</sup> have reported that biopsies taken at the time of surgery from small and large rotator cuff tears ( $n = 40$ ) and compared to rotator cuff tissue taken from control subjects (patients undergoing surgery for traumatic instability,  $n = 4$ ) suggest a different pattern of pathology. The findings revealed an increase in blood vessels, leukocytes, and fibroblasts associated with the small tears, and a decrease in blood vessels, leukocytes, and fibroblasts, together with increased degeneration, edema, amyloid deposition, and chondroid metaplasia associated with the larger tears. No inflammatory cells were identified in the larger tears. There was no correlation between the size of the tears and, age or duration of symptoms. Histological studies of the Achilles, patellar, and lateral epicondylar tendons have also



demonstrated an absence of inflammatory cells.<sup>28–34</sup> The histological evidence suggests that the tendons undergo an intrinsic or internal degeneration involving; deterioration and disorganization of the tendon fiber bundles, increased cellularity (increase numbers of fibroblasts), increase in the amount of proteoglycans (the ground substance/matrix surrounding each individual tendon fiber and tendon bundle), and the formation of new blood vessels (angiogenesis). Sano et al.<sup>35</sup> (1999) have observed large numbers of small blood vessels in the granulation tissue in partial thickness rotator cuff tears, which may represent angiogenesis and attempts at tissue healing. However, it must be recognized that the majority of tendinopathy samples examined are harvested at the time of surgery and subsequently the lack of neutrophils, macrophages, and lymphocytes may be related to the timing of the tissue examination, the chronicity of the condition, and/or any previous pharmacological or nonsurgical treatment.

An understanding of the nature of rotator cuff pathology is further complicated as a result of the poor correlation between macroscopic tendon failure, including partial and full thickness tears, observed in imaging techniques, such as radiographs, diagnostic ultrasound and magnetic resonance imaging, and symptoms.<sup>18–20</sup> As a result of this confusion recent attention has been directed toward the potential role of biochemical mediation of the symptoms, and a number of chemical agents and pathways have been proposed as potential factors involved in tendon pain. Glutamate is a neuropeptide (amino acid) and excitatory neurotransmitter that is involved in the transmission of pain and nociception. In a series of studies, high concentrations of the glutamate were reported in the area of painful Achilles, patellar, and lateral epicondylar tendons.<sup>28–30</sup> However, pain was reported to have decreased and concentrations of glutamate were found to remain the same after an exercise program for the Achilles tendon suggesting that the pain arising from the tendon may not be directly related to the raised glutamate levels.

Angiogenesis occurs as part of the spectrum of pathology in tendinosis. This formation of these new blood vessels is mediated by the cytokines: vascular endothelial growth factor (VEGF), interleukin-1 $\beta$  (IL-1 $\beta$ ), and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ). Cytokines are secreted proteins of small molecular weight that act locally and mediate communication between cells. VEGF expression is induced by hypoxia, and the region around rotator cuff tears is known to be ischemic.<sup>24</sup> These cytokines are known to be involved with tissue inflammation, but in tendinosis they do not appear to be secreted by the cells classically associated with inflammation (neutrophils, macrophages, and lymphocytes) and may be secreted by fibroblasts located in the subacromial bursa,<sup>36</sup> and therefore the classic picture of rotator cuff tendonitis does not

appear to be appropriate. This interpretation of tendon pathology has recently been supported in a tendon overuse study. Perry et al.<sup>26</sup> (2005) reported that cells associated with the classic model of inflammation were not observed in the supraspinatus tendon of rats after running downhill on a treadmill at 17 m/min, for one hour/d, five days a week, for up to 16 weeks. High concentrations of VEGF were observed and were reported to have increased at three days, decreased at one week, and from this point demonstrated a nonlinear increase up to 16 weeks. Prostaglandin E2 (PGE2) is produced from arachidonic acid by means of the activity of cyclooxygenase-2 (COX-2). COX-2 and Von Willebrand Factor (VWF) represent other inflammatory markers and their concentrations were also measured. COX-2 levels were highest after eight weeks of running, but were reported to be relatively low throughout the study. VWF helps platelets to stick to damaged blood vessels and plays a role in homeostasis. VWF was highest at three days, peaked again at eight weeks, and remained elevated during the 16-week investigation. The relationship between PGE2 and tendon disease is uncertain. Alfredson et al.<sup>28–30</sup> reported no increase in the normal concentrations of PGE2 in the area of painful Achilles, patellar, and lateral epicondylar tendons. In contrast, Wang et al.<sup>37</sup> (2004) reported that human patellar tendon fibroblasts subjected to controlled cyclical stretching increased the expression of PGE2 and COX-2. Furthermore, high concentrations of PGE2 in rabbit patellar tendon were associated with hypercellularity, tendon tissue disorganization, and thinner tendon fibrils.<sup>38</sup> The difference in findings between these studies may relate to in vitro and in vivo investigations, different species investigated, as well as the chronicity of the tendon pathology at the time of the investigation.

In rotator cuff disease, the subacromial bursa is thought to be a major source of symptoms.<sup>39</sup> High concentrations of VEGF have been reported in the bursa of patients with rotator cuff disease ( $n = 50$ ), and of clinical relevance, higher concentrations of VEGF correlated with higher pain levels.<sup>40</sup> In addition to this, degenerative changes, a proliferation of fibroblasts and angiogenesis have been observed in the bursa of patients with rotator cuff disease, but infiltrations of polymorphonuclear cells (neutrophils) and plasma cells were not observed<sup>41,42</sup> and as such the concept of a bursal reaction may be more appropriate than the term bursitis.<sup>42</sup>

Together with high concentrations of VEGF, increased concentrations of the inflammatory cytokines IL-1 $\beta$  and TNF $\alpha$  have been reported in the bursa of patients with rotator cuff disease but not in patients with anterior instability of the shoulder.<sup>36,39</sup> Gotoh et al.<sup>39</sup> (2001) suggested that IL-1 $\beta$  produced in the bursa may stimulate peripheral nociceptors leading



to shoulder pain in the absence of inflammatory cells. As with the relationship between VEGF concentration and pain,<sup>40</sup> higher concentrations of IL-1 $\beta$  correlated with higher levels of shoulder pain.<sup>39</sup> Gotoh et al.<sup>39</sup> (2001) did not investigate the concentration of IL-1 $\beta$  from asymptomatic controls, which may have an influence on any conclusions relating to the relationship between the role of interleukin and symptoms, and this would need to be investigated further. In other research, the combination of high concentrations of IL-1 $\beta$  and tendon loading was found to have a more destructive effect on tendon tissue than mechanical loading alone.<sup>43</sup>

Both IL-1 $\beta$  and TNF $\alpha$  play a role in angiogenesis.<sup>44</sup> There is evidence of neural growth in abnormal tendons and this is associated with blood vessels.<sup>45</sup> This neural tissue may be responsible for the pain and reducing the expression of angiogenesis may deprive this neural tissue of its energy supply (oxygen) and be a mechanism of reducing pain. The association between tendon pain and angiogenesis is not absolute as not all painful tendons have evidence of angiogenesis. If future research establishes a correlation between the presence of angiogenesis and tendon pain, then the presence of these new blood vessels and their relationship with sensory nerves may represent a subset of tendon pain that requires a unique method of diagnosis and management.

Angiostatin is a naturally occurring protein that inhibits angiogenesis.<sup>44</sup> N-acetyl-cysteine, is an antioxidant, which is known to promote angiostatin production and vascular collapse.<sup>46</sup> In addition to this, both IL-1 $\beta$  and TNF $\alpha$  increase the formation of PGE<sub>2</sub>; Ralston and Grabowski<sup>47</sup> (1996) and Sakai et al.<sup>48</sup> (2001) have suggested that controlling the expression of these cytokines may be important in reducing shoulder pain associated with rotator cuff disease. Tillander et al.<sup>49</sup> (2001) reported that iatrogenic bursitis (carrageenan injections into the rat shoulder to simulate rotator cuff bursitis) lead to pathological changes in the supraspinatus tendon, which suggests that bursal pathology may lead to tendon pathology.

In an earlier study, Gotoh et al.<sup>50</sup> (1998) reported that high levels of Substance P were identified around blood vessels in the bursa in patients with rotator cuff disease, and that the concentrations of Substance P and the levels of pain were higher in subjects with partial thickness rotator cuff tears than subjects with full thickness tears. Substance P is a positively charged neuropeptide and is involved in relaying sensory information (pain) to the central nervous system from primary afferent pain sensing receptors and plays an effector role in (neurogenic) inflammation (vasodilation, increased vascular permeability, and edema), proliferation, and repair. Substance P evokes the formation of arachidonic

acid and PGE<sub>2</sub>.<sup>51</sup> Substance P may induce the release of IL-1 $\beta$  and TNF $\alpha$ ,<sup>52</sup> and may also induce reactive oxygen species (ROS).<sup>53</sup> Substance P is also associated with a proliferation of fibroblasts<sup>54</sup> and stimulates angiogenesis.<sup>55</sup>

Recently, much attention has been given to the role that oxidative stress might play in a number of musculoskeletal diseases including rheumatoid arthritis, osteoarthritis of the knee, and tendon disease.<sup>56–59</sup> Oxidative stress refers to excessive generation of ROS or free radicals. ROS include ONOO<sup>–</sup> (peroxynitrite), O<sub>2</sub><sup>–</sup> (superoxide), H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide), and the extremely reactive hydroxyl radical (OH), which is thought to be the species responsible for initiating the oxidative destruction of biomolecules. OHs cause the breakdown of the proteoglycan hyaluronic acid.<sup>60</sup> Hyaluronic acid has been shown to be a major proteoglycan in the rotator cuff<sup>61</sup> and is present in much higher concentrations than in other tendons, such as the Achilles. Although free radicals such as O<sub>2</sub><sup>–</sup>, H<sub>2</sub>O<sub>2</sub>, and nitric oxide (NO) are essential for normal function, and are released from phagocytes to attack pathogens, significant increases in the production of ROS occur when the capacity of the antioxidant system to scavenge excess free radicals is exceeded. Sources of ROS include: mitochondria, phagocytosis, ischemia reperfusion after strenuous exercise, smoking, certain antibiotics, and diet. Oxidative stress caused by ROS may lead to cellular damage, and the unsaturated fatty acid components of the cell wall are a major target. ROS may also damage nucleic acid structure, which may compromise cell survival. NO is a diatomic free radical involved, as a signaling molecule, in the regulation of many diverse processes in the body including vascular regulation, fracture healing, sarcomere numbers, tendon repair, and collagen synthesis. NO patches have been shown to reduce pain and improve strength in patients suffering from tennis elbow, and inhibition of NO leads to a significant reduction in cross-sectional area in experimentally injured tendon. Although NO has a beneficial role in many body processes, it is highly unstable and is synthesized via its isoforms (iNOS, eNOS, nNOS) from the amino acid, L-arginine. Once synthesized, NO can react with O<sub>2</sub><sup>–</sup> and produce ONOO<sup>–</sup> (peroxynitrite), which is a powerful oxidant.

Diet appears to influence tendon pathology as a result of oxidative stress. Radak et al.<sup>57</sup> (2002) reported that mature rats fed a restricted diet (decreased free radicals) demonstrated significantly less tendon degeneration in comparison to rats kept on a normal diet. In addition, increased concentrations of free radicals have also been found in synovial fluid of subjects with painful knee osteoarthritis in comparison to asymptomatic controls.<sup>58</sup> Several cytokines, including TNF $\alpha$  are involved in the formation of free radicals. Mendes et al.<sup>62</sup> (2003) reported that IL-1 $\beta$  induces articular chondrocytes to produce



H<sub>2</sub>O<sub>2</sub> and a similar mechanism may exist in the sub-acromial bursa due to the raised IL-1 $\beta$  concentrations (Gotoh et al., 2001).

In summary it appears that high concentrations of the inflammatory cytokines VEGF, IL-1 $\beta$ , and TNF $\alpha$ , as well as increased concentrations of Substance P and possibly PEG2 are associated with tendon pathology. It also appears that high concentrations of oxidants may also be involved in tendon pathology, with cytokines being involved in the formation of oxygen radicals. Therefore, controlling the expression of the inflammatory cytokines and oxidants may be beneficial in reducing pain and disability in patients with rotator cuff disease.

Diets containing differing percentages of types of PUFAs have a clear effect on inflammation. PUFAs are divided into three main categories: n-3, n-6, and n-9. It has been hypothesized that modern western diets often have high concentrations of n-6 animal fatty acids at the expense of n-3 fatty acids derived from plants and marine oils. The ratio of n-6:n-3 PUFA is approximately 25:1 in the modern western diet, whereas it was nearer to 2:1 in preindustrialized societies.<sup>56</sup> The n-6 fatty acids can be subdivided into n-6 animal fatty acids and n-6 gamma-linolenic acid (GLA). GLA is a precursor of prostaglandin E<sub>1</sub>, which, in contrast to PGE<sub>2</sub>, is reported to suppress cytokine formation. The n-3 and n-6 (GLA) fatty acids give rise to less potent inflammatory signal than n-6 animal PUFA.<sup>63</sup> The mechanism by which PUFAs have an anti-inflammatory effect remains uncertain. n-3 PUFA and n-6 GLA PUFA generally reduce the synthesis of IL-1 $\beta$  and TNF $\alpha$ , and n-6 animal PUFA increase the amounts of inflammatory cytokines in the serum, and diets low in n-6 PUFA tend to reduce TNF $\alpha$  formation.<sup>64–67</sup> The formation of IL-1 $\beta$  was reduced in diets low in n-6 PUFA at four weeks, but was found to increase after this time point.<sup>67</sup> These researchers also reported that mice fed n-3 PUFA in the form of fish oil possessed macrophages, which yielded less PGE<sub>2</sub> and TNF $\alpha$ . However, it appears that diets high in n-3 PUFA generate more superoxide, hydrogen peroxide, and NO than in control animals.<sup>67</sup>

Cyclooxygenase enzymes are involved in the production of eicosanoids from arachidonic acid. COX-1 is known for maintaining the integrity of the gastrointestinal lining. Inflammation is associated with up-regulation of COX-2 and increased formation of prostaglandins. Overexpression of COX-2 leads to increased expression of VEGF and angiogenesis. COX-2 expression is stimulated by growth factors and cytokines. Recently, selective COX-2 inhibition has been available. It was manufactured in an attempt to selectively inhibit the effects of COX-2 enzymes, while sparing the effects of COX-1 on eicosanoid synthesis. Reports have emerged that suggest this therapy together with other nonsteroidal

anti-inflammatory medications may have deleterious cardiac side effects.<sup>68</sup> If this is correct, alternative methods of reducing the pain and dysfunction associated with rotator cuff disease must be identified. If it is possible to inhibit COX-2 expression via reducing the synthesis of IL-1 $\beta$  and TNF $\alpha$  by increasing the concentration of n-3 PUFA in the diet, then this may lead to a reduction in PGE<sub>2</sub>.

Mavrogenis et al.<sup>59</sup> (2004) investigated the use of essential fatty acids and antioxidants in the treatment of tendon disorders. In this double-blinded study, 40 recreational athletes with a variety of tendon pathologies were randomized to placebo tablets and 16 treatments of ultrasound, or, tablets containing essential fatty acids (n-3 fatty acids and n-6 GLA fatty acids) and antioxidants and 16 treatments of ultrasound. After 30 days, there was a mean decrease in pain score in 99% of the athletes and 31% of the control group. Although confidence intervals were not reported, the difference in pain levels was statistically significant ( $p < 0.001$ ) in favor of the experimental group. There was an approximate five-point reduction (on a ten-point scale) in pain (SD approximate 1.0) in the experimental group at one month, and an approximate two-point reduction (SD approximate 1.5) in the placebo group. This study provided a valuable insight in the potential of these compounds in the management of tendon pathology. In this study, 20 subjects were randomized to each group (40 in total), nine subjects were lost to follow-up, analysis was based on treatment received and not on the intention-to-treat principle, and final follow-up (subjective pain scores and estimated levels of sports activity) occurred at 32 days. The study group was comprised of tendon pathologies from different regions of the body including the shoulder, elbow, and knee. In the shoulder region, there were 12 subjects in total, ten were diagnosed as having supraspinatus tendinopathy (ten in total, with five in each group), and two as having infraspinatus tendinopathy (two in total, with both in the experimental group). In general, the regional tendon pathologies were not equally distributed between the two groups. No adverse effects were reported by any of the participants in this study. The authors recommended that additional studies are needed to further verify their findings. Additionally, it is not known if the benefit in the experimental group was due to the individually active substances or the combination with ultrasound therapy. It is also not known from this study if the beneficial effect was due to the PUFA or the antioxidants of the combination of both active substances.

## SUMMARY

There is a low-level scientific evidence that suggests the potential benefits of dietary supplementation as an adjunct in the treatment of conditions thought to be



associated with, or mediated by inflammatory cytokines and/or oxidative stress. As such, the potential for dietary supplementation of PUFA and antioxidants to reduce the disability and morbidity associated with rotator cuff tendinopathy and subacromial bursal pathology is appealing but has not yet been formally investigated. Due to the minimal reported adverse side effects of taking PUFA supplements, the risk–benefit ratio is low despite the scant evidence for their efficacy. However, before any recommendations regarding taking dietary supplements for patients with rotator cuff in an attempt to alleviate symptoms, there is a definite need for robust and meaningful clinical research in parallel with a biochemical analysis of the effect of the supplements on this common musculoskeletal problem.

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**R** ORIGINAL ARTICLE

## Shoulder strength testing: the intra- and inter-tester reliability of routine clinical tests, using the PowerTrack™ II Commander

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### Received

Received 19 April 2011;  
accepted 16 September 2011

### Keywords

Reliability, inter-/intra-tester reliability, precision, hand-held dynamometer/dynamometry, muscle strength testing, JTech Commander PowerTrack™ II, shoulder.

### Conflicts of Interest

None declared

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DOI:10.1111/j.1758-5740.2011.00162.x

### ABSTRACT

**Background** To assess intra- and inter-tester reliability of measuring shoulder strength using a new hand-held dynamometer.

**Methods** On two occasions, two examiners (blinded to output) measured seven separate tests of shoulder strength. Twenty-three participants with no shoulder symptoms were tested bilaterally. Each test was performed three times as a 'make test' using a hand-held digital dynamometer.

**Results** Intraclass correlation coefficients (2,1) and (2,3), 95% confidence intervals and standard errors of measurements (SEM) demonstrated good intra- and inter-tester reliability of all tests [ICC(2,3) > 0.87], with the exception of inter-tester reliability of right abduction [ICC(2,3) = 0.77]. Greater reliability of all tests was demonstrated when the mean of three trials was used compared to the first measurement. Intra-tester reliability of all tests using ICC(2,1) ranged from 0.74 to 0.98; ICC(2,3) ranged from 0.89 to 0.98. Inter-tester reliability using ICC(2,1) ranged from 0.52 to 0.94; ICC(2,3) ranged from 0.77 to 0.96. The smallest detectable difference (SDD), used to measure precision, ranged from 5.9 to 12.5 Newtons.

**Discussion** The findings obtained in the present study suggest that using the methods employed in the population investigated demonstrated good to excellent intra- and inter-tester reliability for the measurement of shoulder strength. The SEM and SDD findings provide guidance for values that may be considered as a real change in strength.

### INTRODUCTION

Shoulder pain and weakness are common, with up to one-third of individuals experiencing symptoms in this region during their lives [1,2]. Clinically, pain is typically measured using visual or numerical pain rating scales [3–5]. Muscle strength testing may be performed using manual muscle tests, fixed isokinetic devices, spring weights and pulleys and hand-held dynamometers [6–14]. In the clinical environment, manual muscle testing (MMT) and hand-held dynamometers (HHD) are practical for their simplicity, quick set-up times and transportability. However, MMT is reported to lack sensitivity, is unreliable [15,16] and is confounded by the subjectivity of the testing procedure [17]. MMT do not use measurements of force or weight that may empirically demonstrate improvement of deterioration and has a limited ability to identify small differences in muscle strength [6,17,18]. Studies that have investigated HHD and MMT have reported better reliability with HHD [6,7]. Shoulder strength tests may also be used to monitor the health status of individuals without symptoms, aiming to assess the influence of strength training, disuse and ageing on shoulder force over time. Although reliable, fixed isokinetic devices are impractical for use in many clinical settings as a result of space requirements, set-up

times, portability and financial constraints [8–13]. Muscle strength testing using HHDs has been shown to exhibit good-to-excellent reliability [6,15,19] and may be more sensitive for detecting deficits in shoulder external rotation strength than isokinetic devices [18].

Clinically, shoulder strength testing routinely involves an assessment of shoulder abduction, flexion, internal and external rotation strength, together with elbow flexion (as a result of the multi-articular function of the biceps brachii). Other tests, such as the colloquially named full and empty can tests, are also assessed for pain reproduction and strength deficits. These tests are often used to rule in (and out) a diagnosis of rotator cuff tendinopathy [20,21], which may occur in younger individuals following trauma or overuse, as well as in older individuals with age-related deterioration.

Although clinicians routinely perform a series of strength tests to determine whether there is a uni- or multi-directional pattern of shoulder weakness, no study was identified that has attempted to establish the intra- and inter-reliability of these routine testing procedures. Clinicians would benefit from knowledge of the reliability of the series of clinical tests of strength that they perform.



Many different HHDs are available and have been used in the study of shoulder and elbow flexion strength. One relatively new device, the JTech PowerTrack™ II Commander HHD (JTECH Medical, Salt Lake City, UT, USA), is in common clinical use and is being used to assess the strength in patients with shoulder conditions and to support clinicians' decisions on treatment planning, interventions and outcome. The device has a digital strain-gauge with a digital storable output of strength, measured in Newtons (N) or pounds (lbs). The manufacturers claim that the device is able to maintain 99% accuracy even when the muscle force is applied off centre as a result of the axis compensation 'smart' load cell. Because of its increasing clinical use, clinicians would benefit from knowing how reliable the device is and what are the standard error of measurements when using the device to determine whether a real change has occurred over time or simply as a consequence of intervention. Additionally, because patients, research participants and individuals without symptoms may have their shoulder strength tested by the same assessor or different assessors, knowledge of the intra- and inter-rater reliability would also be beneficial.

As such, the present study aimed to assess the intra- and inter-tester reliability of one maximal isometric voluntary contraction (MIVC) and the mean of three (MIVC) of a sequence of tests of shoulder strength in a group of individuals without shoulder symptoms.

## MATERIALS AND METHODS

### Participants

Twenty-three healthy volunteers (seven males and 16 female; age range 25 years to 73 years), without any history of shoulder pathology were recruited verbally from colleagues and associates. Exclusion criteria were: individuals under 18 years old, a history of shoulder pain, anyone who was unable to give consent, and, for female participants, pregnancy. Potential participants would be excluded if shoulder pain was produced during the Neer Sign, Hawkins' test, resisted external rotation, as well as palpation around the region of the greater tuberosity [22–24]. No participant tested positive and was excluded as a result of these tests.

### Ethics

Permission to conduct the present study was granted by the Biomedical & Health Sciences, Dentistry Sciences & Engineering Research Ethics Sub-Committee, Kings College London, UK. All data collected were confidential and anonymized. Participants all provided their informed consent before their involvement and were aware that they could leave the study at any time.

### Research/study design

The study involved a within-subject, repeated-measures design, designed to test the intra- and inter-tester reliability of a series of tests of shoulder strength.

### Testers

Two physical therapists specializing in musculoskeletal conditions with 10 years (H.D.) and 11 years (F.S.) of experience conducted the

intra- and inter-tester reliability testing. To ensure proficiency with the hand-held dynamometer, both testers underwent a minimum of 3 hours of training with the device.

### Procedure

Participants attended one assessment session, which lasted 150 minutes. Each subject sat on a treatment table (with no back support) with their hips and knees at 90° and their feet flat on a footstool. They were asked to adopt a natural relaxed sitting position of the upper torso. The protocol involved an investigation of seven strength tests: shoulder joint abduction, flexion, full can test, empty can test, external and internal rotation and elbow flexion. To ensure consistency, shoulder and elbow positions were measured using an inclinometer [25,26]. Although it is common to define abduction in the scapular plane as occurring 30° from the sagittal plane, there is difficulty in ensuring this exact angle clinically when re-measuring shoulder abduction that is not in the pure coronal plane at different time points by the same or multiple testers. Additionally, anatomical studies have demonstrated substantial variations in the humeral shaft retroversion angle (average 20° to 30°; range 20° to 55°) and the angle of retroversion of the glenoid fossa on the scapula [27–32], as well as substantial variations in scapular and thoracic posture [33–35], which would influence the true plane of scapular motion. Accordingly, to improve the consistency of repeated measurements, the angle half way between the coronal and sagittal planes (i.e. 45° from each) was chosen to be the range abduction measured in the present study.

The position of the shoulder and elbow, as well as inclinometer placement, stabilization procedures, HHD placement, investigator positioning and direction of force, are detailed in Table 1.

All tests were measured bilaterally using the JTech PowerTrack™ II Commander HHD. The device may be used with either a concave or a flat curved testing surface. For participant comfort, the concave surface was chosen. The force produced is calculated and automatically displayed on the digital console. To ensure accuracy, the PowerTrack™ II and Commander consoles were factory calibrated and, when turned on, the console automatically calibrates itself. Two devices (HHDA and HHDB) were used in the investigation. Each participant was tested with the same device. Sixteen participants were tested with HHD A and seven subjects with HHD B.

Each test was performed as a 'make' test (i.e. a maximal contraction exerted against a stationary dynamometer) and repeated three times in a standardized sequence with a 5-second rest between tests. Strength was measured in Newtons (N). A stopwatch was used to ensure a 5-second rest period between tests, that each isometric contraction lasted for 5 seconds and that each phase lasted for 15 minutes. Each phase was then repeated on the contralateral shoulder. Each sequence, involving both shoulders, was repeated alternately by both investigators so that each participant would undergo a total of four sequences on each shoulder. A wash-out period of 15 minutes was given before the contralateral shoulder was retested. The order of investigators and the order of shoulder testing were randomized by a computer generated randomization chart.

**Table 1** Testing positions for hand-held dynamometry

Muscle test	Inclinometer placement	Testing position of limb	Manually stabilized body part to maintain position	Dynamometer placement	Position of investigator	Direction of force applied by investigator
Shoulder abduction	Proximal part of inclinometer placed at deltoid insertion on lateral aspect of upper arm along shaft of humerus	Elbow extension, shoulder 10° abduction	Medial epicondyle	Lateral aspect of humerus, just proximal to the elbow	Lateral to subject, stride standing	Medially directed force, perpendicular to limb
Shoulder flexion	Proximal part of inclinometer placed at deltoid insertion on anterior aspect of upper arm along shaft of humerus	Elbow extension, shoulder 10° flexion	Posterior elbow	Anterior aspect of humerus, just proximal to the elbow	Anterior to subject, stride standing	Anterior to posterior force, perpendicular to limb
Full can test	Proximal part of inclinometer placed at deltoid insertion on anterior aspect of upper arm along shaft of humerus	Elbow extension, upper limb 90° elevation in scapular plane (45° to coronal plane), forearm pronated with upper limb internally rotated	Anterior elbow	Volar aspect of the forearm just proximal to volar wrist crease	Lateral and posterior to limb	Downward force, perpendicular to limb
Empty can test	Proximal part of inclinometer placed at deltoid insertion on anterior aspect of upper arm along shaft of humerus	Elbow extension, upper limb 90° elevation in scapular plane (45° to coronal plane), forearm supinated with upper limb externally rotated	Posterior elbow	Dorsal aspect of the forearm just proximal to dorsal wrist crease	Lateral and posterior to limb	Downward force, perpendicular to limb
Shoulder external rotation	Distal part of inclinometer placed at lateral wrist crease along radius	Upper arm in a neutral position at trunk, elbow flexed to 90°, forearm in a neutral position so palm facing inwards	Medial wrist	Dorsal aspect of forearm with distal part of pad at dorsal wrist crease	Lateral to subject, stride standing	Medially directed force, perpendicular to limb
Shoulder internal rotation	Distal part of inclinometer placed at lateral wrist crease along radius	Upper arm in a neutral position at trunk, elbow flexed to 90°, forearm in a neutral position so palm facing inwards	Medial wrist	Volar aspect of forearm with distal part of pad at volar wrist crease	Medial to limb, lateral to subject, stride standing	Laterally directed force, perpendicular to limb
Elbow flexion	Distal part of inclinometer placed at lateral wrist crease along radius	Upper arm in a neutral position at trunk, elbow flexed to 90°, forearm supinated	Posterior wrist	Volar aspect of forearm with distal part of pad at volar wrist crease	Lateral to subject	Downward force, perpendicular to limb

Starting position: relaxed sitting with upper limbs by side, elbows extended.



Standardized instructions were read out to each participant during each contraction: 'hold it there, don't let me move you (2 seconds), now push as hard as you can, keep pushing, keep pushing and relax (3 seconds)' [36]. The investigator stopped the resistance as the word 'relax' was said. All resistance was provided with the examiner's dominant hand.

Before and after the procedure, each subject was asked to rate any pain using the verbal numerical rating scale [3–5]. Measurements of muscle force displayed on the console were recorded for each test by two independent observers. The investigators and subjects were blinded to the results obtained. The independent observers also monitored the time taken between tests and sequences.

### Sample size

For a true reliability of 0.8 against an alternative reliability of 0.9, based on a 5% significance level and a power of 80% ( $\beta = 20$ ), for two testers, 46 subjects were required [37]. Twenty-three subjects were used in the present study and measurements were taken bilaterally, producing a sample size of 46.

### Reliability and precision analysis

Reliability was determined using a combination of intraclass correlation coefficients (ICC), 95% confidence intervals (95% CI), standard error of measurement (SEM) and the smallest detectable difference (SDD) [38]. ICC values above 0.75 were considered as indicative of good reliability and those above 0.91 to be excellent reliability [38]. The 95% CI were calculated for both ICC(2,1) and ICC(2,3). This allowed determination of the reliability of obtaining one measurement of strength in comparison to the mean of three measurements. Knowledge of the one-SEM value provides the clinician with 68% confidence that the true measurement obtained lies two SEM above or below the obtained measurement, and two SEM provides 95% confidence [38]. The SDD at the 0.05 level was calculated as;  $1.96 \times \sqrt{2\text{SEM}}$  [39,40]. The SDD provides evidence of the smallest degree of change between two measurements that could be considered statistically significant [39]. This was therefore calculated for the inter-tester measurements. Two-tailed paired samples *t*-tests were applied to the results to establish any significant differences between the single, first measurements and the mean of three measurements within and between examiners. The data were analyzed using SPSS, version 14 (SPSS, Woking, UK).

### RESULTS

After obtaining informed consent, 23 individuals without shoulder pain participated in the present study. There were 16 females (70%) and seven males (30%), with a mean (SD) age of 37 years (35.4 years) and range of 22 years to 73 years. Mean (SD) height was 173.4 cm (17.68 cm) and range of 163 cm to 188 cm. Mean (SD) weight was 69.9 kg (30.4 kg) and range of 52 kg to 95 kg. Mean (SD) body mass index was 23.2 kg/m<sup>2</sup> (7.1 kg/m<sup>2</sup>) and range of 18.4 kg/m<sup>2</sup> to 28.4 kg/m<sup>2</sup>. Three (13%) participants were retired, 39% (*n* = 9) were in the medical profession and 48% (*n* = 11) worked principally at a desk. Seventeen percent (*n* = 4) of participants performed no regular activity, six individuals (26%) walked more than 45 minutes daily, 31% (*n* = 7) participated in

cardiovascular activities one to three times each week and 26% (*n* = 6) participated in cardiovascular activities four times each week. Twenty (87%) individuals were right-hand dominant and three (13%) were left handed.

The ICC(2,3) results demonstrated better reliability than the ICC(2,1) results for all intra-tester reliability measurements. This suggests that the mean of three strength tests using this device produces better reliability than one single test. The one exception to this was the reliability of right shoulder internal rotation (for Tester 2) where the reliability of one test was equal to the mean of three (ICC = 0.98). The intra-rater ICC(2,3) results for both testers were excellent for all tests, with the exception of left shoulder flexion [Tester 1, ICC(2,3) = 0.89], right shoulder full can test [Tester 1, ICC(2,3) = 0.90] and right shoulder flexion [Tester 2, ICC(2,3) = 0.89]. The two-SEM results ranged from 12.5 N (empty can test, right side) to 31.6 N (shoulder flexion, left side) for Tester 1, and, for Tester 2, from 8.9 N (empty can test, left side) to 24.9 N (elbow flexion, left side) and (shoulder flexion, right side). The mean of three measurements [ICC(2,3)] produced better reliability than one test of strength [ICC(2,1)] for the inter-tester trail. All tests were found to have excellent reliability [ICC(2,3)  $\geq$  0.91], with the exception of left and right side shoulder abduction [left shoulder; ICC(2,3) = 0.87, right shoulder; ICC(2,3) = 0.77]. The SDD ranged from 5.9 N (empty can test, right shoulder) to 12.5 N (elbow flexion, right side). The two-SEM results ranged from 8.9 N (empty can test, right side) to 40.9 N (elbow flexion, right side).

Table 2 details the results for strength (N) for each of the tests. Figure 1 details the mean results for strength (N) for the individual tests for each tester. Table 3 details the results for the intra-tester reliability. Table 4 details the results for the inter-tester reliability.

### DISCUSSION

The evaluation of shoulder flexion, abduction, internal and external rotation strength, the full and empty can tests, as well as the strength of elbow flexion, are routinely performed as part of an examination of shoulder function. Clinically, if available, the strength of the symptomatic shoulder is usually compared to the asymptomatic side. Additionally, investigations of the effect of strength training as well as inactivity, or those investigating changes in strength over time, such as may occur with ageing, and the effect of medications (such as statins) or co-morbidities (such as type II diabetes), require knowledge of the reliability of strength testing of individuals without any current shoulder symptoms. In clinical practice and research studies, more than one assessor may test shoulder strength and, because of this, knowledge of inter-tester reliability is important.

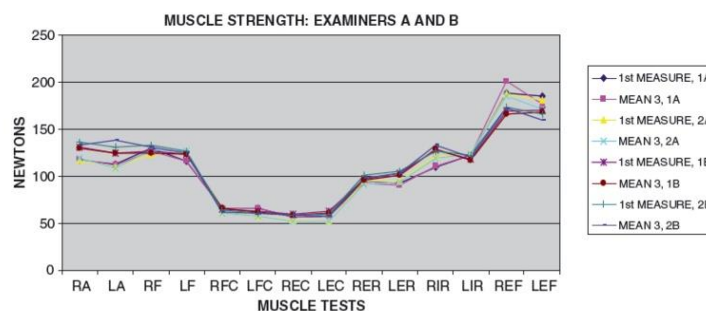
No previous study was identified that has measured both the intra- and inter-rater reliability for a routine battery of commonly used clinical tests of shoulder strength using the JTech PowerTrack PowerTrack™ II Commander HDD. This is important because this HDD is in common clinical use. Encouragingly, the findings of the present study support those of other investigations of other reliability trials of testing shoulder strength using hand-held dynamometers [6,9,41–43]. However,

**Table 2** Results for strength for each of the tests measured in Newtons (N)

	Test									
	Abduction Newtons (SD) range		Flexion Newtons (SD) range		Full can Newtons (SD) range		Empty can Newtons (SD) range		External rotation Newtons (SD) range	
	Right side	Left side	Right side	Left side	Right side	Left side	Right side	Left side	Right side	Left side
Tester 1 (HD)										
First of first 3	117.4 (33.5)	112.9 (35.1)	129.3 (51.1)	116 (40.9)	65.6 (39.9)	66.1 (40.9)	56.7 (24.9)	57.8 (29.5)	94.4 (38)	92.9 (45.6)
	60.1 to 195.7	62.3 to 186.8	62.3 to 269.1	69 to 215.7	17.8 to 164.6	31.1 to 155.7	28.9 to 120.1	17.8 to 115.7	55.6 to 184.6	44.5 to 186.8
Mean of first 3	117.9 (36.9)	111.5 (39.9)	126.5 (48.8)	115.6 (40.0)	65.7 (37)	65.7 (38.5)	56.6 (24.8)	57.4 (29.6)	92.2 (43.9)	90.7 (49.1)
	60.1 to 224.6	44.5 to 200.2	57.8 to 269.1	60 to 229.1	15.6 to 180.2	26.7 to 155.7	26.7 to 120.1	13.3 to 115.7	48.9 to 186.8	44.5 to 200.2
First of second 3	117.2 (32.1)	109.5 (33.3)	123.8 (44.4)	125.6 (50.8)	63 (31)	57.7 (33.5)	53.5 (25.1)	52.5 (25.3)	94.4 (35.8)	94.7 (44.6)
	75.6 to 182.4	64.5 to 177.9	64.5 to 264.7	73.4 to 267	26.7 to 129	22.4 to 133.5	22.2 to 109	24.5 to 115.7	51.2 to 177.9	48.9 to 191.3
Mean of second 3	118.9 (37.1)	108.5 (36.2)	128.1 (48.3)	126.4 (54.7)	60.6 (29.2)	57.8 (32.2)	51.7 (22.8)	51.7 (23.3)	91.2 (35.9)	93.3 (46.7)
	71.2 to 220.2	46.7 to 213.5	51.2 to 264.7	68.9 to 282.5	26.7 to 133.5	20 to 133.5	20 to 109	20 to 115.7	44.5 to 177.9	42.3 to 222.4
Tester 2 (FS)										
First of first 3	130.9 (25.0)	124.4 (33.9)	126.8 (37.3)	123.6 (40.0)	64.7 (34.8)	62.9 (37.5)	59.6 (25.8)	62.7 (28.1)	97.2 (30.7)	103.1 (38.5)
	89.0 to 193.5	62.3 to 195.7	75.6 to 233.5	71.2 to 206.8	35.6 to 169	24.5 to 153.5	26.7 to 106.8	31.1 to 131.2	62.3 to 186.8	55.6 to 262.4
Mean of first 3	129.9 (29.0)	124.6 (37.1)	124.2 (37.2)	123.0 (41.9)	65.6 (33.5)	61.6 (36.9)	58.9 (25.4)	60.5 (27.2)	95.3 (31.8)	100.6 (48.4)
	77.8 to 220.2	62.3 to 242.4	75.6 to 233.5	66.7 to 242.4	31.1 to 173.5	26.7 to 173.5	26.7 to 113.4	22.2 to 131.2	60.1 to 211.3	55.6 to 237.9
First of second 3	135.9 (33.3)	130.6 (28.9)	132.9 (37.7)	126.4 (39.4)	63.9 (29.1)	61.1 (34.8)	58.9 (23.6)	59.7 (27.0)	101.2 (38.4)	105.6 (51.1)
	84.5 to 222.4	71.2 to 204.6	73.4 to 231.3	66.7 to 213.5	33.4 to 131.2	28.9 to 155.7	28.9 to 115.7	26.7 to 122.3	57.8 to 195.7	66.7 to 231.3
Mean of second 3	132.8 (31.4)	138.5 (33.1)	130.3 (39.2)	124.2 (38.7)	62.1 (28.1)	60.5 (34.4)	58.3 (22.2)	57.3 (24.7)	97.5 (35.2)	102.8 (48.3)
	77.8 to 222.4	71.2 to 364.8	66.7 to 242.4	66.7 to 229.1	26.7 to 131.2	24.5 to 155.7	28.9 to 115.7	24.5 to 122.3	55.6 to 195.7	60.1 to 262.4

SD, standard deviation.





**Fig. 1** First measure, 1A = First measurement Sequence 1 Examiner A – HD. First measure, 1B = First measurement Sequence 1 Examiner B – FS. First measure, 2A = First measurement Sequence 2 Examiner A – HD. First measure, 2B = First measurement Sequence 2 Examiner B – FS. LA, left shoulder abduction; LEC, left empty can test; LEF, left elbow flexion; LER, left shoulder external rotation; LER, left shoulder internal rotation; LF, left shoulder flexion; LFC, left full can test. Mean 3, 1A = Mean of three trials Sequence 1 Examiner A – HD. Mean 3, 1B = Mean of three trials Sequence 1 Examiner B – FS. Mean 3, 2A = Mean of three trials Sequence 2 Examiner A – HD. Mean 3, 2B = Mean of three trials Sequence 2 Examiner B – FS. RA, right shoulder abduction; REC, right empty can test; REF, right elbow flexion; RER, right shoulder external rotation; RF, right shoulder flexion; RFC, right full can test; RIR, right shoulder internal rotation. Mean results for strength (Newtons) for each test for the two examiners.

as a result of different devices being tested using different research protocols, extrapolating the findings between studies is difficult.

Using the HHD in the positions tested, good to excellent levels of intra- and inter-tester reliability were found for both the intra- and inter-rater reliability. Consistent with other investigations of the reliability of shoulder measurements [26,34,35,44], the findings of the present study demonstrated that inter-tester reliability was lower than intra-tester. In the present study, the mean of three tests produced better reliability than one single measurement. With respect to the intra-tester reliability trial, the smallest two-SEM (8.9 N) was for the empty can test on the left side (Tester 2). This suggests that the clinician may be 95% confident that the true measurement of strength would be within a range of values from 8.9 N below to 8.9 N above the measurement for strength obtained. The largest two-SEM was 31.6 N for left shoulder flexion strength (Tester 1). The mean flexion strength for the two examiners for the test of left shoulder flexion strength was 122.3 N. If this was the value found in a clinical assessment of left shoulder flexion strength, for 95% confidence, a clinician should predict that the true value for shoulder strength would lie between 90.7 N and 153.9 N. Clinicians and researchers may assess changes in strength following intervention, during disease progression and to determine the influence of ageing. This finding suggests that if baseline left shoulder flexion strength was found to be 122.3 N, a clinician/researcher would not be certain any real change had occurred until it had decreased to 90.7 N or increased to 153.9 N. For the smallest 2SEM results the implication would be that for the left shoulder empty can test with a mean starting point of 56.8 N a clinician/researcher would not be certain of any real change until force production had decreased to 47.9 N or increased to 65.7 N.

The reliability of using a HHD in measuring the strength of shoulder abduction has been examined previously [9,42,45]. The

majority of studies assessing the strength of shoulder abduction did so in the scapular plane and at varying angles of elevation: 30°, 60°, 120° (24), 45° (18) and 90° (7, 11). No consensus has emerged regarding the most appropriate testing position and, clinically, many individuals with shoulder symptoms and asymptomatic individuals with substantial weakness are incapable of maintaining higher ranges of shoulder elevation. To date, no study has tested shoulder abduction at 10°, which may be used clinically because it is often a relatively pain free position of the shoulder. Shoulder flexion is another movement that is routinely assessed and, similarly, no consensus has emerged as to the most appropriate testing position. In the current investigation, shoulder flexion strength was tested at 10° of flexion. When tested in these positions, the intra-tester reliability [ICC(2,3)] for right and left shoulder abduction and flexion ranged from very good to excellent (0.89 to 0.97). The inter-tester reliability [ICC(2,3)] ranged from good (0.77) to excellent (0.92).

Internal and external rotation strength is universally tested as part of the routine shoulder protocols. Using the method employed in the present study, both intra- and inter-tester reliability [ICC(2,3)] was found to be excellent, ranging from 0.92 to 0.94 for inter-tester reliability and 0.95 to 0.98 for intra-tester reliability. Comparable findings have been reported previously. Hayes et al. reported ICC values of 0.85 to 0.92 for intra-tester reliability and 0.82 to 0.85 for inter-tester reliability [6]. Leggin et al. reported very good to excellent reliability for both tests [9]. However, Hayes et al. [6] investigated research participants in a supine position, which is not always employed clinically and, although there were similarities between the findings of the present study and the findings reported by Leggin et al. [9], a different HHD was tested (Nicholas HHD) and a different statistical analysis was used. The findings of previous research and those of the present study provide a growing body of evidence for the reliability of assessing shoulder strength using a HHD. However, pooling of

**Table 3** Results for the intra-tester reliability

	Test											
	Abduction			Flexion			Full can			Empty can		
	Right side	Left side	Right side	Right side	Left side	Left side	Right side	Left side	Left side	Right side	Left side	Left side
<b>Tester 1 (HD)</b>												
Mean of all six trials												
Newtons	118.4	109.9	127.4	121	63.2	61.8	54.9	54.6	91.7	92.2	114.8	123.3
(SD)	(32.9)	(37.5)	(47.6)	(45.8)	(33.4)	(35.6)	(25)	(26.5)	(37)	(45.8)	(51.2)	(64.1)
Range	60.1 to 224.6	44.5 to 213.5	51.2 to 269.1	60.1 to 282.5	15.6 to 180.2	20 to 155.7	20 to 120.1	13.3 to 115.7	44.5 to 186.8	42.3 to 222.4	42.3 to 220.2	46.7 to 293.6
Single measure												
ICC(2,1)	0.74	0.83	0.84	0.76	0.84	0.92	0.83	0.87	0.94	0.96	0.9	0.94
95% CI	0.48 to 0.88	0.65 to 0.92	0.66 to 0.93	0.51 to 0.89	0.65 to 0.93	0.74 to 0.97	0.65 to 0.92	0.70 to 0.94	0.86 to 0.97	0.91 to 0.98	0.72 to 0.96	0.87 to 0.97
Average measure												
ICC(2,3)	0.94	0.94	0.97	0.89	0.9	0.96	0.94	0.93	0.97	0.98	0.97	0.98
(95% CI)	0.86 to 0.98	0.86 to 0.98	0.89 to 0.98	0.62 to 0.92	0.78 to 0.96	0.85 to 0.99	0.85 to 0.98	0.83 to 0.97	0.93 to 0.99	0.96 to 0.99	0.92 to 0.99	0.96 to 0.99
SEM (Newtons)	8.45	9.34	8.45	15.6	10.7	7.1	6.2	7.1	6.2	6.7	8.5	9.3
SEM from ICC(2,3)	16.46	18.24	16.46	31.6	20.9	14.2	12.5	14.2	12.9	13.3	17.4	18.2
2SEM from ICC(2,3)												
<b>Tester 2 (FS)</b>												
Mean of all six trials												
Newtons	140.5	126.3	127.3	123.6	63.8	61	60.9	58.9	96.4	101.7	127	118.5
(SD)	(29.4)	(34.3)	(37)	(39.6)	(30.9)	(35.6)	(23.6)	(26)	(34.5)	(33.8)	(48.5)	(57.4)
range	77.8 to 222.4	62.3 to 251.3	66.7 to 242.4	66.7 to 242.4	26.7 to 173.5	22.2 to 173.5	26.7 to 115.6	22.2 to 173.5	55.6 to 211.3	55.6 to 186.8	60.1 to 238	53.5 to 240.2
Single measure												
ICC(2,1)	0.80	0.78	0.76	0.84	0.9	0.95	0.89	0.92	0.89	0.9	0.98	0.92
(95% CI)	0.59 to 0.91	0.58 to 0.91	0.51 to 0.89	0.67 to 0.93	0.78 to 0.96	0.88 to 0.98	0.77 to 0.95	0.87 to 0.97	0.77 to 0.95	0.79 to 0.96	0.95 to 0.99	0.84 to 0.97
Average measure												
ICC(2,3)	0.93	0.92	0.89	0.92	0.95	0.98	0.96	0.97	0.96	0.95	0.98	0.97
(95% CI)	0.85 to 0.97	0.81 to 0.97	0.74 to 0.95	0.82 to 0.97	0.88 to 0.98	0.96 to 0.99	0.90 to 0.98	0.92 to 0.99	0.90 to 0.98	0.87 to 0.98	0.97 to 0.99	0.94 to 0.99
SEM (Newtons)	7.56	9.79	12.5	11.6	7.1	4.9	7.1	4.5	7.1	7.6	6.7	8.5
SEM from ICC(2,3)	15.12	19.57	24.9	22.7	13.8	10.2	13.8	8.9	13.8	15.1	13.8	17.4
2SEM from ICC(2,3)												

CI, confidence interval; ICC, intraclass correlation coefficient; SD, standard deviation; SEM, standard error of measurement.



**Table 4** Results for the inter-tester reliability

Abduction		Flexion		Full can		Empty can		External rotation		Internal rotation		Elbow flexion	
		Right side	Left side	Right side	Left side	Right side	Left side	Right side	Left side	Right side	Left side	Right side	Left side
Single measure													
ICC(2,1)		0.52	0.77	0.84	0.83	0.94	0.93	0.87	0.93	0.84	0.86	0.84	0.84
95% CI		0.16 to 0.76	0.48 to 0.89	0.67 to 0.93	0.65 to 0.93	0.87 to 0.98	0.85 to 0.97	0.71 to 0.94	0.82 to 0.97	0.66 to 0.93	0.42 to 0.95	0.62 to 0.93	0.65 to 0.93
Average measure													
ICC(2,3)		0.77	0.87	0.91	0.92	0.97	0.96	0.97	0.96	0.92	0.93	0.91	0.93
(95% CI)		0.45 to 0.91	0.63 to 0.95	0.79 to 0.96	0.82 to 0.97	0.92 to 0.99	0.92 to 0.99	0.93 to 0.99	0.92 to 0.99	0.81 to 0.97	0.57 to 0.98	0.68 to 0.97	0.83 to 0.97
SEM (Newtons)													
SEM from ICC(2,3)		15.1	13.8	12.9	11.6	6.2	7.6	4.5	5.8	10.2	12.9	20.5	19.6
2SEM from ICC(2,3)		30.7	27.6	25.8	23.1	12.5	15.1	8.9	11.6	20	25.8	40.9	39.6
SDD (Newtons)		10.8	10.3	9.9	9.4	6.9	7.6	5.9	6.7	8.8	9.9	12.5	12.2

CI, confidence interval; ICC, intraclass correlation coefficient; SDD, smallest detectable change; SEM, standard error of measurement.

The testing positions described for testing the strength of elbow flexion are more consistent. The majority of studies testing elbow strength have done so with the subject sitting, elbow at side of body, and elbow flexed to 90° forearm supinated [9,13,41,42]. However, Stratford and Balsor tested elbow flexion in a supine position [13]. Kendall et al. suggest that elbow flexion could be tested in a sitting or supine position [46]. In the present study, both intra- and inter-tester reliability was found to be excellent, with values ranging from 0.96 to 0.98 for intra-tester scores and 0.91 to 0.94 for inter-tester findings. Again, knowledge of the two-SEM values is important because it will guide clinicians and researchers with respect to knowing whether real change has occurred. The findings of the present study suggest that the mean of three tests is more reliable than one test. Other trials of strength testing have reported that the results of one trial may be sufficient [47,48] and this would certainly save clinical time. Differences may relate to the different methods employed as well as the regions tested.

The authors were unable to find a study that has investigated the intra and inter-rater reliability of the empty can and full can tests. This is surprising as these procedures are used routinely within clinical practice to aid in diagnosing rotator cuff pathology [20]. In this study we chose to investigate these tests in a wide age range of participants as both young and older individuals may present with pathology of these structures. The present study established excellent intra-tester reliability for the full can test with ICC(2,3) results ranging from 0.90 to 0.96, and very good to excellent reliability (0.89 to 0.94) for the empty can. Of note, these tests were associated with the lowest force production of all the strength tests evaluated and the smallest SEM. Comparably the inter-tester reliability [ICC(2,3)] was excellent for these two tests, with values ranging from 0.96 to 0.97, and again with the lowest SEM values.

It is important to have knowledge of measurement reliability for shoulder strength for a given population. This allows a comparison of strength production over time to determine whether an exercise programme or intervention leads to an alteration in strength.

It also allows for a determination of the effect of strength as a result of reduced activity, ageing, as well as the influence of co-morbidities and pharmacological side effects. The reliability of a measurement also provides confidence when obtaining normative data in a given population to compare with another population. However, a limitation of the present study is that the data were only obtained from individuals without symptoms, such that no knowledge is available regarding the reliability of using the methods investigated in the present study in a population of individuals with specific or generic shoulder symptoms.

The measurement of shoulder strength is routinely assessed in individuals with and without shoulder symptoms. For a given method, it is necessary to establish the reliability of that procedure. The findings obtained in the present study suggest that, using the

methods employed in the population investigated, the hand-held JTech PowerTrack™ II Commander HDD demonstrated good to excellent intra- and inter-tester reliability for the measurement of shoulder strength. The mean of three tests was found to produce more reliable measurements than just one measurement. The SEM findings provide guidance for values that may be considered as a real change in strength. Further research is required to determine the intra- and inter-tester reliability in symptomatic individuals.

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